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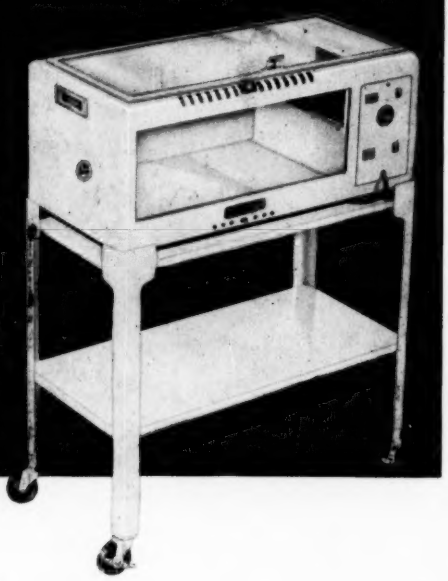

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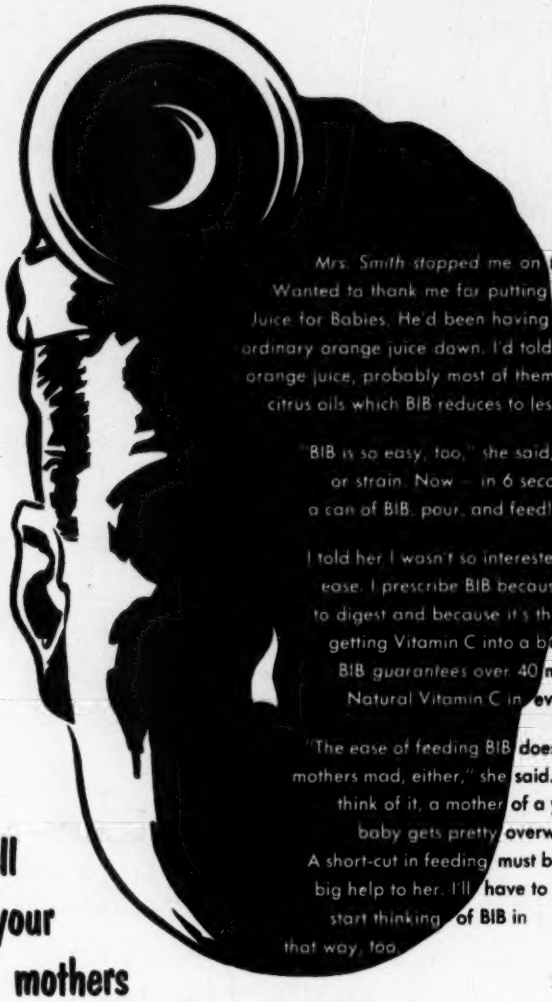

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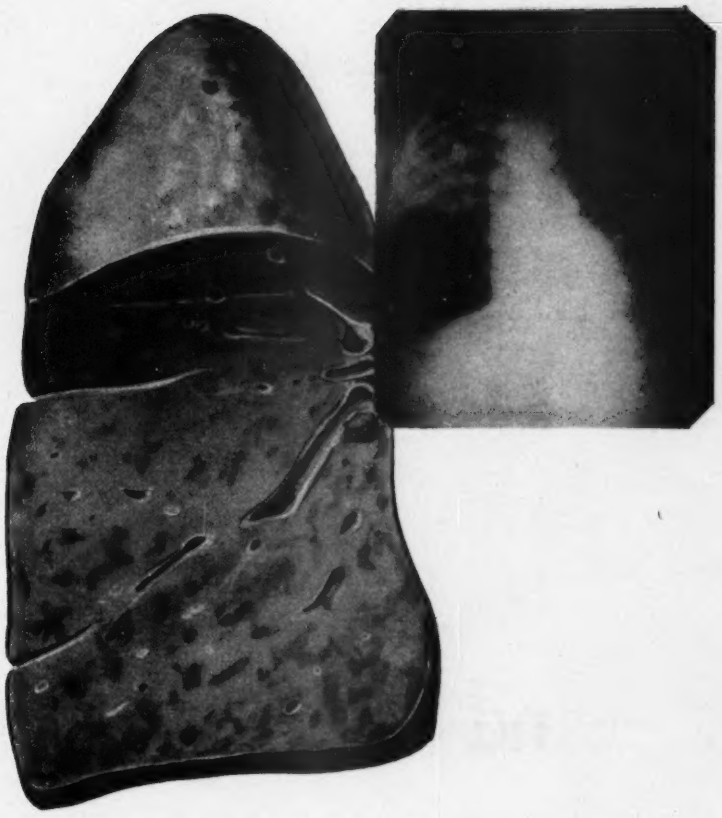

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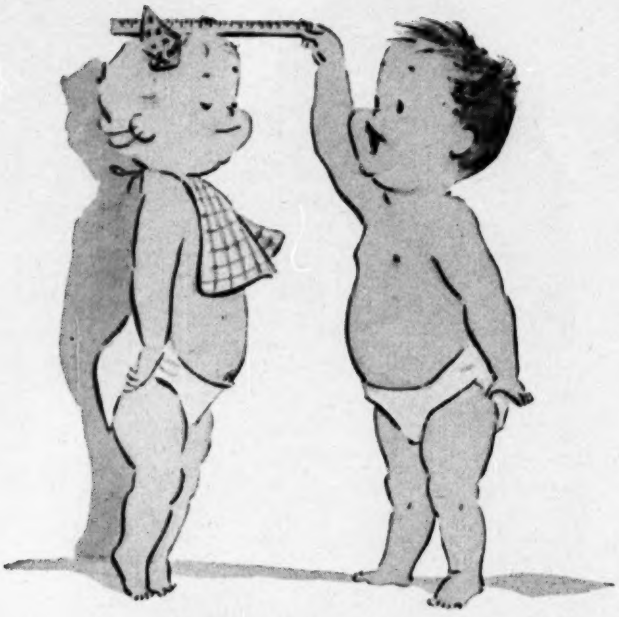

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*Clein, N. W.: Cow's Milk Allergy in Infants, *Annals of Allergy*, March-April, 1951.

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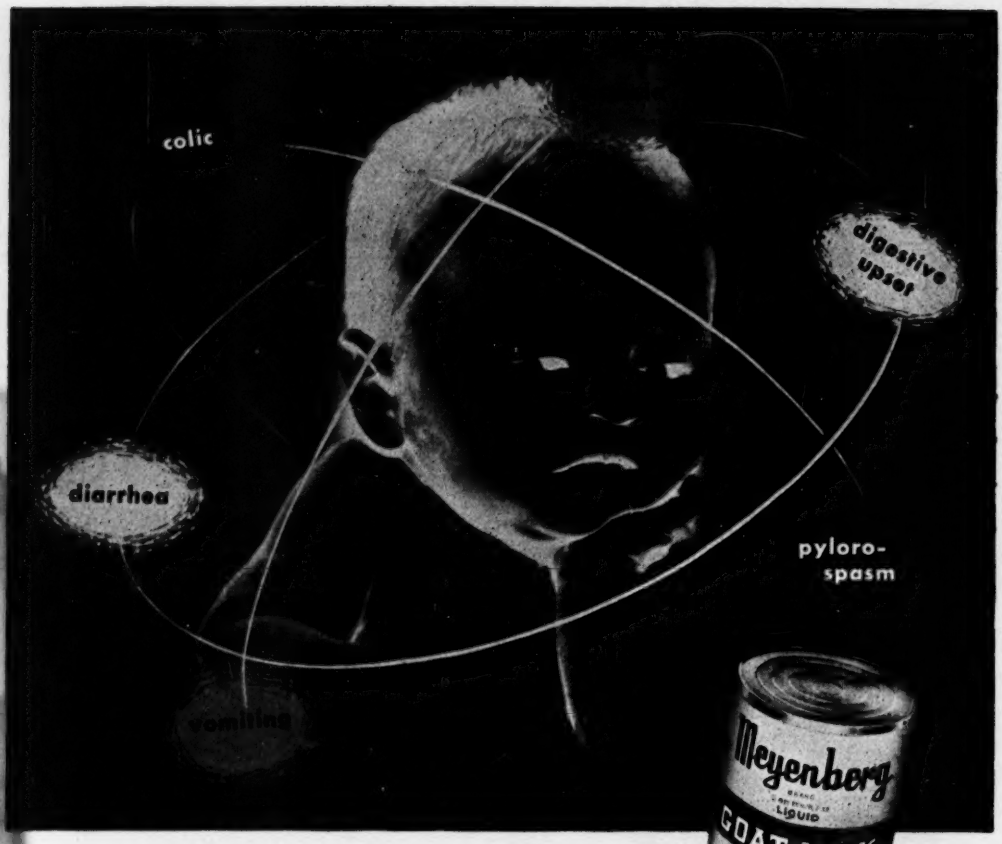

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CONTENTS

PAGE

Use of Wetting Agents in the Treatment of Respiratory Infections of Infants. GLENN C. HALL JR., M.D., CHARLOTTESVILLE, VA. 1

Importance of Rest in the Treatment of Early Convalescent Poliomyelitis. WALLACE GREEN, M.D., NEW YORK 4

Prophylactic Immunization and Poliomyelitis. JAN LIEBEN, M.D., HARTFORD, CONN. ... 8

Fanconi Syndrome: Multiple Congenital Anomalies with Hypoplastic Anemia. HENRY K. SILVER, M.D.; WILLIAM C. BLAIR, M.D., AND C. HENRY KEMPE, M.D., SAN FRANCISCO 14

Gamma Globulin Studies in Tuberculosis in Children. BENJAMIN M. LEVIN, M.D.; HARRY KAUFMAN, M.D., AND JESUS DE LA HUERGA, M.D., CHICAGO 26

A Community Study of Rheumatic Fever. HOWARD A. JOOS, M.D., AND CHRIS P. KATSAMPES, M.D., ROCHESTER, N. Y. 37

CASE REPORTS:

Sclerema Neonatorum Successfully Treated with Corticotropin (ACTH). NORMAN KENDALL, M.D., AND SEYMOUR LEDIS, M.D., PHILADELPHIA 52

PROGRESS IN PEDIATRICS:

Factors to Be Considered in Planning a Premature Center. HELEN M. WALLACE, M.D.; MARGARET A. LOSTY, R.N., AND LEONA BAUMGARTNER, M.D., NEW YORK .. 54

SOCIETY TRANSACTIONS:

Society for Pediatric Research 65

ABSTRACTS FROM CURRENT LITERATURE 92

DIRECTORY OF PEDIATRIC SOCIETIES 142

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A. M. A.
American Journal of Diseases of Children

VOLUME 83 JANUARY 1952 NUMBER 1

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USE OF WETTING AGENTS IN THE TREATMENT OF RESPIRATORY INFECTIONS OF INFANTS

GLENN C. HALL Jr., M.D.
CHARLOTTESVILLE, VA.

THERE has long been a need for intense moisture in certain respiratory infections of infants. Among these are laryngotracheobronchitis, bronchiolitis, and laryngeal diphtheria. This necessary degree of moisture is often difficult to obtain by using the average croup tent. Steam has the disadvantage of producing hyperpyrexia in the already feverish infant. The use of wetting agents was first attempted at the University of Virginia Hospital in late 1949, and we have continued this work during the last two years.

Wetting Agents Used and Their Manufacturers

Product	Type	Manufacturer
(1) Duponol C *.....	Sodium lauryl sulfate	E. I. Dupont de Nemours and Company
(2) Aerosol OS *.....	Alkylaryl sulfonate	American Cyanamid Company
(3) Tergitol 08 *.....	Synthetic primary alcohol sulfate	Union Carbide and Carbon Corporation
(4) Aerosol MA *.....	Sulfonated ester of dicarboxylic acid	American Cyanamid Company

* Registered trademark.

There are several agents available at the present time. They are not, however, manufactured for clinical use and can be obtained only for experimental investigation. The table enumerates four of the commoner ones.

Morris [1] gave an excellent chemical review of these agents from the medical standpoint. Briefly, they contain two radicals: (1) a long hydrocarbon chain, which is the hydrophobic group, and (2) a short -SO_4Na group, which is the hydrophilic group. When these compounds are dissolved in water, the hydrophilic group becomes aligned on the surface next to the water, and the hydrophobic group becomes directed upward toward the overlying gas. As a result, the surface is covered with an oil-like film and has a much lower surface tension than water alone. One can readily appreciate the value of such a mechanism in aiding an infant with a weak cough reflex, overwhelmed by a thick, tenacious exudate.

From the Department of Pediatrics, University of Virginia Medical School.

1. Morris, G. E.: Brief Review of Chemistry of Wetting Agents, J. Indust. Hyg. & Toxicol. 26:175 (May) 1944.

TOXICITY

The toxicity of these compounds was thoroughly investigated from a systemic standpoint by Gershenfeld and Witlin [2] and from the pulmonary standpoint by myself.[3] I observed that toxic manifestations could be avoided by controlling the concentration of these agents. Toxicity in guinea pigs consisted of degeneration and desquamation of alveolar epithelium. There was often invasion of alveolar spaces by macrophages. All of these toxic changes could be prevented by keeping the concentration of the wetting agent below 0.1%.

The possibility of an allergic reaction to one of these agents must be kept in mind. However, one would not expect a young infant to be allergic to an extrinsic agent which he had not been in contact with previously. Certainly these agents should not be used more than once without patch testing the child beforehand.

METHODS

Our clinical experience has been limited to the use of one of these agents, namely, sodium lauryl sulfate (duponol C®). This compound is dissolved in distilled water so as to obtain a concentration of 0.05%. This solution is then placed in the humidifier bottle of a croup tent, in this case a Croupette Humidity and Oxygen Tent.[4] The solution is dispersed with oxygen or some other source of pressure if oxygen is not indicated. A fog immediately forms, the density of which is controlled by the oxygen flow.

INDICATIONS AND RESULTS

These agents are indicated whenever intense moisture is necessary. We have made use of one of them in the treatment of acute laryngotracheobronchitis, bronchiolitis, laryngeal diphtheria, and in other similar conditions. The results have been gratifying; however, improvement following the use of sodium lauryl sulfate has been difficult to evaluate, as one can well appreciate with a therapeutic drug of this nature. Twenty patients have received this wetting agent. There were no fatalities or adverse reactions. Included in this series were five cases of laryngotracheobronchitis, two cases of diphtheria, and five cases of bronchiolitis.

REPORT OF CASES

CASE 1.—A 7-week-old white girl was admitted to the University of Virginia Hospital with a three-day history of cough, wheezing, and cyanosis. Physical examination on admission revealed a normal temperature, severe respiratory distress with rapid respirations and many fine rales over both sides of the chest. X-ray examination of the chest gave negative results except for moderate emphysema. A diagnosis of bronchiolitis was made, and administration of penicillin and aureomycin was begun. The patient was also placed in a croup tent and received moisture and oxygen. However, the infant's condition became progressively worse. Sodium lauryl sulfate, in a 0.05% concentration, was added to the Croupette Tent reservoir, and definite improvement was promptly noted. Recovery was uneventful.

CASE 2.—A 3-year-old white girl was admitted to the University of Virginia Hospital with a 24-hour history of fever, sore throat, difficult breathing, and wheezing. Physical examination on admission revealed a temperature of 100.4 F. rectally, pulse rate 160, and respirations 42 a minute. The child was in severe respiratory distress with an inspiratory stridor. The throat was

2. Gershenfeld, L., and Witlin, B.: Surface Tension Reducents in Bactericidal Solutions: Their in Vitro and in Vivo Efficiencies, Am. J. Pharm. **113**:215 (June) 1941.

3. Hall, Glenn C.: Pulmonary Toxicity of Wetting Agents Dispersed as Aerosols, Am. J. Dis. Child. **80**:408 (Sept.) 1950.

4. Manufactured by Air-Shields, Inc., Hatboro, Pa

very boggy, but there was no membrane present. A diagnosis of laryngotracheobronchitis was made, and treatment was instituted immediately. This consisted in administration of streptomycin and aureomycin. The patient was placed in a croup tent and received moisture and oxygen. The condition of the patient became worse, and tracheotomy was considered. However, it was decided that a wetting agent would be tried first, and sodium lauryl sulfate, in a 0.05% solution, was added to the Croupette Tent reservoir. In a few hours the patient was greatly improved. Convalescence was uneventful.

CASE 3.—A 3-year-old white boy was admitted to the University of Virginia Hospital with a two-day history of croupy cough and fever. Physical examination on admission revealed a temperature of 102 F. rectally, pulse rate 160, and respirations 22 a minute. The patient was acutely ill, with marked hoarseness and retraction of the soft tissues of the chest with inspiration. There was a grayish-white membrane over both tonsils and extending to the adjacent pharyngeal wall. Throat culture was positive for Corynebacterium diphtheriae. Treatment consisted in administration of 30,000 units of diphtheria antitoxin and penicillin. Respirations became more difficult, and tracheotomy was considered. However, after the addition of sodium lauryl sulfate in the proper concentration to the reservoir, the child improved, and tracheotomy was postponed. Recovery was uneventful.

SUMMARY AND CONCLUSIONS

The use of a new method for producing intense moisture in the treatment of certain acute respiratory infections of infants is presented. Wetting agents are thought to be of help in the management of acute laryngotracheobronchitis, laryngeal diphtheria, and bronchiolitis. The toxicity of these agents and the possibility of allergic reactions are discussed. Several case reports are presented.

The results of the use of wetting agents in exudative respiratory infections of infants have been encouraging enough to warrant their investigation in other medical centers. They should be used only in well-selected cases and in the proper concentration.

IMPORTANCE OF REST IN THE TREATMENT OF EARLY CONVALESCENT POLIOMYELITIS

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IN THE accepted definition of the term, there is no known "cure" for poliomyelitis. During the early convalescent stage when the greatest amount of recovery is taking place, various forms of treatment are being employed, the particular modality chosen and championed being a personal choice rather than one scientifically proved to be the most efficacious.

There are those who lay great stress upon pool therapy to promote coordinated joint motion. Others emphatically decry the use of underwater therapy, claiming such activity leads to rapid fatigue and harmful substitution, and they stress selective muscle reeducation with the patient on a table. There are those who are enthusiastic advocates of electrical stimulation for muscle reeducation and prevention of loss of tone in involved muscles, and there are others who object to the use of electrical stimulation on the ground that paretic muscles are thereby rapidly overfatigued. There are those who employ drugs such as curare and mephenesin (tolserol®) to decrease muscle spasm and more rapidly bring the patient to the point where physical therapy may be instituted, and there are others who claim they find no real value in drugs and rely solely upon hot packs. In recent years the trend toward earlier ambulation in the management in surgical cases has crept into the armamentarium of treatment in early convalescent poliomyelitis. There are those who recommend walking with or without crutches, supervised and unsupervised, up to the point of exhaustion, on the premise that such activity promotes more rapid return of muscle power.

Out of such a welter of treatments, each with its strong adherents and opponents, must come the realization that none is specific; that as anterior horn cells recover, muscle power spontaneously returns and that a form of therapy must be chosen which impedes this natural recovery as little as possible.

To approach the problem of therapy rationally, it is important to reiterate certain well-known and fundamental pathophysiological facts relative to poliomyelitis. First, paralysis is due to involvement of anterior horn cells. Second, as of today, there is no therapy, pharmacological or physical, which will modify the amount of destruction of these cells or enhance their recovery. An involved anterior horn cell has one of three fates: It might be rendered physiologically inactive by local inflammation of that portion of the spinal cord where it resides, in which case in a brief period measured in days, when the inflammation subsides, the cell regains

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The observations reported in this paper were made when the author during the poliomyelitis epidemic in North Carolina in 1948 served as orthopedic surgeon at the Ellen Fitzgerald Emergency Poliomyelitis Unit, located in Monroe, N. C.

its function and muscle power returns. The anterior horn cell might be itself directly attacked by the virus and undergo degeneration, which, however, is only moderate in degree, in which case such degeneration is reversible, and after a period measured in months, probably not more than three, it recovers and muscle power returns. Or, finally, the anterior horn cell might be so severely inflamed by the virus that it undergoes irreversible degeneration, in which case no type of therapy, regardless of how intense or prolonged, will result in return of power in its related muscle units.

This paper, based upon personal daily supervision of over 200 patients in the early convalescent stage of poliomyelitis during a recent epidemic, is written to minimize the value of any specific form of active therapy and to emphasize the importance of the unheroic and unglamorous role of rest.

Very early in the epidemic I was impressed by the deleterious effect of overactivity. On rounds, patients were ambulated to observe their gait, the object being that of instruction to test how accurately a diagnosis of specific muscle involvement could be made through analyzing pathological gait. It was noted that the longer the patient was ambulated, the worse became the gait. A patient with moderate involvement at the start of ambulation might walk with an imperceptible limp, and then as ambulation continued a progressively worse gait would develop.

Being preoccupied with analyzing pathological gaits, I failed to realize the implications of what had been observed; it was the casual remark of a physical therapist which prompted a more careful appraisal of the effect of overactivity. In discussing a patient who that morning had been ambulated to the point of marked instability and on whom a muscle evaluation had been performed in the afternoon, six hours later, the therapist had noted that power in the involved gluteus medius was markedly decreased in comparison with an evaluation performed the previous week. The following day I myself checked muscle power before ambulation and again much later in the day and proved to my own satisfaction that in a significant number of cases there was an appreciable decrease in muscle power as a result of excessive ambulation. The decrease in muscle power was much greater and much more prolonged than could be explained on the basis of local increase in metabolites, as is the commonly accepted explanation for fatigue in normal muscle. I did not then know nor do I yet know the reasons for the phenomenon observed, but having on hand an unusually large number of patients in the early convalescent stage of poliomyelitis, I realized the opportunity for clinical observations upon groups of patients with nearly similar involvement in order to study the effect of activity versus rest. Accordingly, patients were placed upon one of three regimens: (1) unrestricted ambulation and tricycle riding; (2) ambulation and tricycle riding for three one-hour periods daily, and (3) bed rest except for a brief period of physical therapy daily.

Groups one and two received the same physical therapy as the third, namely, selective muscle reeducation alternately on a table or in a Hubbard Tank and manipulation of each joint through its normal range of motion. Patients in all three groups when in bed were maintained in neutral joint alignment.

It was noted that the most consistent improvement occurred among patients in the group that was kept at rest except for a brief daily period of supervised muscle reeducation. It was noted that the least amount of improvement and in many cases regression occurred among patients in the group allowed unlimited

activity. In the latter group it was further noted that patients tended to acquire persistent pathological gaits; smaller children especially, once they had acquired the knack of stabilizing themselves through a pathological gait, would do so too in order to delay fatigue.

One case was convincing evidence of the futility of overactivity and the beneficial effects of rest. The patient, a young man, two weeks after the febrile stage had moderate, diffuse involvement of both lower extremities. He was treated at home and being anxious to recover his muscle power, cooperated wholeheartedly with instructions, which were to ambulate to the point of fatigue, rest briefly, and then continue ambulating. Before this regimen was instituted, the patient could walk unaided about his room. After a week, during which time he had become progressively weaker, he was able to walk only if supported by two people. The patient was hospitalized, and a muscle survey revealed few muscles which could function against gravity. He was kept at absolute bed rest except for a brief daily period of selective muscle reeducation and passive movement of all his joints, and within a short time the majority of muscles in his lower extremities were able to function against moderate resistance.

Immediately after the febrile stage it is no problem to keep the patient in bed. Only those patients with minimal muscle involvement express any intense desire to escape from the boredom of such confinement. Though the acute stage is generally characterized by only a low-grade fever of short duration, nevertheless the disease produces an inordinate amount of generalized debilitation. The patients are content to lie in bed in whatever apparatus is used to prevent gross malalignment of involved extremities. After their daily bath and the changing of their bed linen, they frequently are so exhausted that they drop off to sleep.

Several weeks later when strength returns and they begin to take a keener interest in their environment, it frequently becomes a task of no mean proportions to enforce bed rest. The adventitious movements made in bed are more than sufficient to prevent loss in muscle tone, and the direction of the problem lies not in encouraging activity but rather in degressing it in order to conserve strength. Toward this end the aid of the family and the women of the community were enlisted. Radios, phonographs, group singing, amateur and semiprofessional vaudeville, and movies were scheduled regularly. Occupational therapy and continuation of schooling combined with the above filled out the patient's day, kept minds stimulated, and made easier the onerous task of enforcing bed rest.

It was particularly difficult, considering the nature of poliomyelitis and its psychological impact, upon the patient, the family, the community, the trained and semitrained personnel who were all desperately eager to engage and cooperate in any form of intense active therapy, to insist upon a regimen involving primarily rest. In these days, when fund-raising campaigns for poliomyelitis and general rehabilitation are constantly before the public, to advocate rest as the prime treatment lays one open to criticism at the best of lagging behind modern techniques and at the worst, as actually did happen on several occasions, of having a callous disregard for the welfare of unfortunately stricken patients.

Skeletal deformities were prevented by maintaining neutral alignment of involved extremities and by putting each joint through its normal range of motion daily. To maintain awareness of muscle action, selective muscle reeducation was carried out for a half-hour period daily. It was to the natural recuperative powers of the

anterior horn cells that the greatest credit went for increase in muscle power. The only method which consistently decreased power in an already paretic muscle, outside of permitting it to be overstretched by a more powerful antagonist, was to exhaust the muscle through overactivity.

The literature on muscle physiology relative to poliomyelitis leaves unanswered the question of whether overactivity of a paretic muscle has any more serious effect than a transient loss in power which is made up when adequate rest is enforced. Considering the possibility that there might have been, it was unthinkable to subject patients to a regimen which might have permanent deleterious effects. Experimentation must be carried out in the laboratory to answer this crucial question. If it should be proved that overactivity of a regenerating anterior horn cell will flood that cell with metabolites which it is unable adequately to dispose of and that a persistent accumulation of such metabolites will permanently destroy the already weakened cell, then we must revise drastically our treatment in the early convalescent stage of poliomyelitis.

I had ample convincing evidence on clinical grounds that overactivity produced not greater strength but greater weakness and that enforced bed rest interrupted only by brief daily periods of physical therapy provided the most conducive setting for spontaneous recovery of muscle power.

SUMMARY

When to increase the activities of a patient in the early convalescent stage of poliomyelitis and especially when to allow ambulation depend upon fine judgment, and no categorical time limit can be set. The effects of increased activity and ambulation must be carefully appraised by frequent muscle examination and observation of gait.

Experience gained in supervising the treatment in a large number of such cases was convincing that increasing the activity of patients in the early convalescent stage of poliomyelitis and permitting them to ambulate never succeeded in hastening the return of muscle power but frequently retarded it and led to harmful substitution.

PROPHYLACTIC IMMUNIZATION AND POLIOMYELITIS

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DURING the 1949 poliomyelitis epidemic in Melbourne, Australia, McCloskey[1] became interested in the relationship between poliomyelitis and immunizations. Frequently parents of poliomyelitis patients raised the question of whether an immunization against whooping cough or diphtheria shortly before the onset of poliomyelitis might have brought on the disease.

McCloskey inquired into the history of immunization of 340 poliomyelitis victims. He found 31 children had been immunized within three months of onset. Paralysis was distinctly more frequent in the inoculated than in the uninoculated limbs. On more precise analysis of the time relationship, he found that the interval between the last inoculation and onset of symptoms ranged from 5 to 32 days in all except two of his 31 patients, whose interval was approximately 60 days. From the evidence collected, he concluded that there was a significant relationship in a number of cases between prophylactic injections and the subsequent development of paralytic poliomyelitis during the epidemic. McCloskey rejects the theory that contamination of the syringe or immunization material might be the cause of the subsequent paralysis. He favors the hypothesis that local trauma was responsible in activating and localizing the virus already in the central nervous system.

Similar studies with almost identical conclusions were reported by Martin and also by Geffen[2] in London. More recently, Hill and Knowelden[3] published a careful statistical analysis of data obtained during the 1949 epidemic in England and Wales and included comparisons with a selected control group.

Each of these studies shows that the usual 1:2 or 1:3 ratio of arm to leg paralysis[4] was reversed in groups of children who received prophylactic injections, predominantly in the arm, within the 28-day period prior to the onset of the disease and that the limb recently inoculated was more frequently paralyzed than other limbs.

After the above findings were reported, inquiries were received from physicians by the Connecticut State Department of Health concerning whether or not to

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Epidemiologist, Connecticut State Department of Health.

1. McCloskey, B. P.: The Relation of Prophylactic Inoculations to the Onset of Poliomyelitis, Lancet **1**:659-663 (April 8) 1950.

2. Geffen, D. H.: The Incidence of Paralysis Occurring in London Children Within Four Weeks After Immunization, M. Officer **83**:137-140 (April 8) 1950.

3. Hill, A. B., and Knowelden, J.: Inoculation and Poliomyelitis: A Statistical Investigation in England and Wales in 1949, Brit. M. J. **2**:1-6 (July 1) 1950.

4. Poliomyelitis and Prophylactic Immunization, editorial J. A. M. A. **144**:240 (Sept. 16) 1950. Top, F. H.: Handbook of Communicable Diseases, ed. 2, St. Louis, C. V. Mosby Company, 1947, p. 556.

continue immunizations during the poliomyelitis season. Several physicians even went so far as to suspend immunizations during the summer months. It was decided to undertake a study to determine if Connecticut findings would support the Australian and British views.

The records obtained by the Connecticut State Department of Health on every case of poliomyelitis in the State were supplemented with questions regarding any recent immunizations, with particular attention to the site, the date of immunization, and the material used.

The study was started in July, 1950, and 411 poliomyelitis patients were questioned concerning immunization within 90 days of the onset of their disease. Ninety-eight patients were questioned by the two epidemiologists of the state department of health, and others by local health officers and public health nurses.

Of the 411 patients on whom data were obtained, for 24 it was stated that there had been immunizations within the 90 days prior to the onset of the illness. All those who had had immunizations were contacted by the epidemiologists; the date and site of the immunizations were verified, and the material used was ascertained.

TABLE 1.—*Materials Used for Immunizations*

Diphtheria and tetanus toxoids with pertussis vaccine combined, alum precipitated	8	10
Diphtheria and tetanus toxoids with pertussis vaccine combined, plain	1	
Diphtheria and tetanus toxoids with pertussis vaccine combined, type unknown	1	
Tetanus toxoid, alum precipitated	4	5
Tetanus toxoid, type unknown	1	
Pertussis vaccine, alum precipitated		2
Diphtheria toxoid, alum precipitated		1
Diphtheria and tetanus toxoids, alum precipitated		1
Smallpox vaccine		2
Tetanus antitoxin		2
Rocky Mountain spotted fever vaccine		1

In each case the physician who had given the immunization was questioned, and the date, site, and material were confirmed from his records (Table 1).

(In two cases, namely, 119 and 253, the type of toxoid, whether alum precipitated or not, could not be obtained, as immunization was given out of the state.)

Table 2 shows that of the 10 patients immunized with diphtheria and tetanus toxoids with pertussis vaccine combined, four showed paralysis in the limb receiving the injection, which in each case was an arm.[5] For three of these patients the interval between the immunization and the onset of the illness was 14 to 18 days, and for the fourth the interval was 81 days. Among these 10 patients, there were only two with leg paralysis, one with bulbar paralysis, and three with nonparalytic poliomyelitis. There was an apparent complete reversal of the usual 2:1 leg:arm paralysis ratio in these cases.

Among the five patients receiving tetanus toxoid injections, there was not a single instance of spinal poliomyelitis. Three, however, had bulbar poliomyelitis, and two had the nonparalytic type. Whether this high incidence of bulbar poliomyelitis among those immunized with tetanus toxoid is of special significance or not will be determined when the results of other[6] studies are available for com-

5. Paralysis, in this study, is arbitrarily defined to include muscle weakness lasting for more than four weeks.

6. Korns, R. F.: Health in New York State: Parenteral Injections and Paralysis, Health News **27**:13 (Oct.) 1950.

parison and a larger series of cases have been studied. (One of the patients with bulbar poliomyelitis also had a tonsillectomy 46 days before onset of the poliomyelitis.) The time intervals between date of injection and onset of poliomyelitis

TABLE 2.—*Immunization Within Ninety Days of Onset of Poliomyelitis**

Case No.†	Age of Patient	Days Between Last Injection and Onset of Symptoms	Limb Last Inoculated	Paralysis in Inoculated Limb	Paralysis in Any of 4 Limbs				Type of Poliomyelitis	Other Injections
					RA	LA	RL	LL		
Diphtheria and tetanus toxoids with pertussis vaccine combined (10 cases)										
127	9	47	RA	0	0	0	0	0	Bulbar	Diphtheria-tetanus-pertussis injection, 69 days before onset, left arm
166	4½	14	LA	+	0	+	0	0	Spinal	Diphtheria-tetanus-pertussis injection, 35 days before onset, left arm
304	1	60	RA	0	0	0	0	+	Spinal	Diphtheria-tetanus-pertussis injection: 142 days before onset, left arm; 111 days, right arm
395	1¼	18	LA	+	0	+	0	0	Spinal	Diphtheria-tetanus-pertussis injection, 59 days before onset, right arm
253	11/12	51	A	0	0	0	0	0	Nonparalytic	.....
306	5	83	A	0	0	0	0	0	Nonparalytic	Diphtheria-tetanus-pertussis injection, 106 days before onset, arm
309	10/12	81	RA	+	+	0	0	0	Spinal	Diphtheria-tetanus-pertussis injection, 89 days before onset, right arm; smallpox vaccine, 13 days before onset, left arm
361‡	7	17	A	0	0	0	+	+	Spinal	.....
431	6	64	A	0	0	0	0	0	Nonparalytic	Diphtheria-tetanus-pertussis injection, 86 days before onset, arm
479	1	14	LA	+	0	+	0	0	Spinal	No additional injection given
Tetanus toxoid (5 cases)										
119‡	9	73	LA	0	0	0	0	0	Nonparalytic	.....
108‡	8	49	LA	0	0	0	0	0	Bulbar	.....§
262	11	11	A	0	0	0	0	0	Bulbar	Tetanus injection, 41 days before onset, arm; diphtheria toxoid, 73 days before onset, arm
274	8	5	LA	0	0	0	0	0	Nonparalytic	Tetanus antitoxin, 31 days before onset
246‡	13	7	LA	0	0	0	0	0	Bulbar	Weekly hay fever injections prior to onset
Tetanus antitoxin (2 cases)										
84	5	58	RA	0	0	0	+	+	Spinal	.....
111	17	11	LA	0	0	0	0	0	Nonparalytic	.....
Pertussis vaccine (2 cases)										
107‡	10	12	LA	0	0	0	0	+	Spinal	.....
230‡	10	14	LA	+	0	+	0	0	Spinal	Penicillin, 1 day after onset, buttocks
Diphtheria toxoid (2 cases)										
256	2½	7	RL	+	0	0	+	0	Spinal	No additional injections given
345 ‖	11/12	15	RA	0	0	0	0	+	Spinal	Diphtheria-tetanus toxoid, 49 days before onset, left arm
Smallpox vaccine (2 cases)										
331	5	21	RA	0	0	0	0	0	Nonparalytic	.....
104	4½	15	LA	0	0	0	0	0	Nonparalytic	Simultaneous tetanus injection
Rocky Mountain spotted fever vaccine (1 case)										
86	8	19	A	0	0	0	+	+	Spinal	Penicillin, after onset, both buttocks

* A indicates arm; RA, right arm; LA, left arm; RL, right leg; LL, left leg.
† Case numbers in bold face indicate those cases in which there was subsequent paralysis in the inoculated limb.
‡ The injection given was a booster dose.
§ Patient had a tonsillectomy 46 days before onset.
‖ For this patient the diphtheria toxoid was combined with tetanus toxoid.

for the five patients who had tetanus immunizations were 73 and 5 days for those with nonparalytic poliomyelitis and 7, 11, and 49 days for those with bulbar poliomyelitis.

No special findings were elicited for the two patients given injections of tetanus antitoxin. Both patients received their injections in the arm. However, one of them showed paralysis in both legs. Of the two patients immunized with pertussis vaccine, one had paralysis in the inoculated limb with the onset of his illness following injection within 14 days, and the other had paralysis in the left leg and no paralysis in the inoculated arm. The patient immunized with diphtheria toxoid injected into his right leg showed paralysis in this limb. In Case 345 the patient had been given

TABLE 3.—*Immunization Within Thirty Days of Onset of Poliomyelitis**

Case No.†	Age of Patient	Days Between Last Injection and Onset of Symptoms	Limb Last Inoculated	Paralysis in Limb Inoculated	Paralysis in Any of 4 Limbs RA	LA	RL	LL	Type of Poliomyelitis	Other Injections
Diphtheria and tetanus toxoid with pertussis vaccine combined (4 cases)										
106	4½	14	LA	+	0	+	0	0	Spinal	Diphtheria-tetanus-pertussis injection, 35 days before onset, left arm
395	1¼	18	LA	+	0	+	0	0	Spinal	Diphtheria-tetanus-pertussis injection, 59 days before onset, right arm
361‡	7	17	A	0	0	0	+	+	Spinal	.....
479	1	14	LA	+	0	+	0	0	Spinal	No additional injection given
Tetanus toxoid (3 cases)										
262	11	11	A	0	0	0	0	0	Bulbar	Tetanus injection, 41 days before onset, arm; diphtheria toxoid, 73 days before onset, arm
274	8	5	LA	0	0	0	0	0	Nonparalytic	Tetanus antitoxin, 31 days before onset
246‡	13	7	LA	0	0	0	0	0	Bulbar	Weekly hay fever injections prior to onset
Tetanus antitoxin (1 case)										
111	17	11	LA	0	0	0	0	0	Nonparalytic	.....
Pertussis vaccine (2 cases)										
107‡	10	12	LA	0	0	0	0	+	Spinal	.....
230‡	10	14	LA	+	0	+	0	0	Spinal	Penicillin, 1 day after onset, buttocks
Diphtheria toxoid (2 cases)										
256	2½	7	RL	+	0	0	+	0	Spinal	No additional injection given
345§	11/12	15	RA	0	0	0	0	+	Spinal	Diphtheria-tetanus toxoid, 49 days before onset, left arm
Smallpox vaccine (2 cases)										
331	5	21	RA	0	0	0	0	0	Nonparalytic	.....
104	4½	15	LA	0	0	0	0	0	Nonparalytic	Simultaneous tetanus injection
Rocky Mountain spotted fever vaccine (1 case)										
86	8	19	A	0	0	0	+	+	Spinal	Penicillin, after onset, both buttocks

* A indicates arm; RA, right arm; LA, left arm; RL, right leg; LL, left leg.
† Case numbers in bold face indicate those cases in which there was subsequent paralysis in the inoculated limb.
‡ The injection given was a booster dose.
§ For this patient the diphtheria toxoid was combined with tetanus toxoid.

an injection with combined diphtheria and tetanus toxoids in the right arm, but the paralysis was in the left leg rather than the right arm, which received the injection.

In both patients immunized with smallpox vaccine the disease showed a nonparalytic course.

The patient immunized with Rocky Mountain spotted fever vaccine had paralysis in both legs but no paralysis in the arm receiving the injection.

In summary, among the 24 patients reported as having had immunizations, six were paralyzed in the inoculated limb. Five of these had the immunization within

18 days before the onset of poliomyelitis and one within 81 days before the onset. Five were immunized in the arm and one in the leg. Six of the immunized patients had leg paralysis in the limb which did not receive the injection, which gives a 1 : 1 ratio instead of the usual 1 : 2 or 1 : 3 ratio for arm versus leg paralysis. There are four bulbar poliomyelitis cases in the group, and in three of these tetanus toxoid was given. Eight of the 24 immunized patients had nonparalytic poliomyelitis (Tables 2 and 3).

In Table 2, which includes all patients, it is shown that six of 24 immunized patients became paralyzed in the limb receiving the injection, which is a ratio of 1 : 4. Examination of Table 3, which includes only patients immunized 30 days

TABLE 4.—*Type of Poliomyelitis and Paralysis in an Immunized and a Nonimmunized Group*

Type of Poliomyelitis	Nonimmunized Group		Immunized Group	
	No.	%	No.	%
Nonparalytic	98	58.0	8	33.3
Bulbar	14	8.3	4	16.7
Arm monoplegia	4	2.4	5	20.8
Arm diplegia	5	2.9	0	....
Leg monoplegia	31	18.3	4	16.7
Leg diplegia	5	2.9	3	12.5
Triplegia	3	1.8	0	....
Quadriplegia	6	3.6	0	....
Hemiplegia	3	1.8	0	....
Total	169	100.0	24	100.0

TABLE 5.—*Comparison of Arm: Leg Paralysis by Age Distribution in an Immunized and a Nonimmunized Group*

Age, Yr.	Immunized			Nonimmunized		
	Total	Arms	Legs	Total	Arms	Legs
0-4	7	4	3	8	4	4
5-9	3	0	3	12	1	11
10-14	2	1	1	7	2	5
15-19	0	0	0	18	2	16
Total	12	5	7	45	9	36

before onset, reveals that five of the 15 patients showed paralysis in the limb receiving the injection, which is a ratio of 1 : 3. This higher incidence of paralysis in the limb receiving the injection in those patients immunized within the incubation period of the disease was noticed by the Australian and British authors, too.

COMPARISON OF AN IMMUNIZED WITH A NONIMMUNIZED GROUP

In order to compare the incidence of arm and leg paralysis in our immunized group with that in a representative group of nonimmunized patients, data from a random sample of 169 nonimmunized, 1950, Connecticut poliomyelitis patients were analyzed. The site of paralysis and age distribution were compared with those in the immunized group.

If we examine Table 4, we find the greatest difference between immunized and nonimmunized groups in the arm monoplegias—2.4% against 20.8%. However, if we compare the age distribution of the immunized group with that of the non-

immunized group and their paralyses, this difference becomes less striking, as shown in Table 5, which compares arm and leg paralysis subdivided by age. Only two of the 12 immunized spinal poliomyelitis patients were older than 10 years; seven were under the age of 5.

In the youngest age group, 0 to 4 years, there were seven patients with four arm paralyses and three leg paralyses in the immunized group and eight patients with four arm paralyses and four leg paralyses in the nonimmunized group—practically identical numbers. Hemiplegias, triplegias, and quadriplegias were omitted from the comparison table because there were no comparable cases in the immunized group. Five of our six patients who had paralysis in the inoculated limb were in the 0 to 4 year age group.

McLeod,[7] in his report of the 1950 Belfast polio epidemic, notes an equally high incidence of arm paralysis in the 0 to 1 year age group irrespective of whether the patient had been immunized or not.

COMMENT

The high incidence of arm paralysis in the 0 to 4 year age group, immunized or nonimmunized, makes one wonder how much location of subsequent paralysis is influenced by previous immunization. The question also arises of why there should be such a high incidence of arm paralysis in this particular age group. It may be because infants use their arms about as much as their legs, whereas older children use their legs much more than their arms.

Although there seemed to be a higher incidence of spinal paralysis in the immunized group (50%) as compared with the nonimmunized group (33%), it is disputable whether this difference warrants such stringent measures as postponing immunization for whooping cough and diphtheria for six months during a poliomyelitis epidemic year, which, as it happens, the last three years have been. Is the risk of paralysis greater than that of whooping cough and diphtheria and tetanus?

SUMMARY

Of 24 immunized patients, nine were in the 0 to 4 year age group; five of the six patients who had paralysis in the inoculated limb were in the 0 to 4 year age group, and in four of these patients paralysis had occurred in the inoculated arm. Comparison of these data with those from a nonimmunized group of 169 patients shows that arm paralysis occurred just as frequently as leg paralysis at that age and not at the ratio of 1 : 2 or 1 : 3, as found when figures of arm : leg paralyses in all age groups are analyzed together. No definite conclusions can be drawn from the small number of cases available, but the high incidence of arm paralysis in the 0 to 4 year age group should definitely be considered in studies of this kind.

7. McLeod, W. J.: Poliomyelitis in Belfast, Brit. M. J. **1**:736-738 (April 7) 1951.

FANCONI SYNDROME

Multiple Congenital Anomalies with Hypoplastic Anemia

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THE FANCONI syndrome is an unusual combination of findings which include severe progressive refractory macrocytic anemia with pancytopenia (i.e., anemia, neutropenia, and thrombopenia), a hypoplastic bone marrow, and a generalized brown, melanin-like pigmentation of the skin, associated with congenital defects which have varied somewhat from case to case, but have often included microcephaly, bone abnormalities—particularly of the forearms and thumbs—hypogenitalia, genitourinary tract abnormalities, strabismus, and in at least one case, unilateral deafness, gynecomastia, and congenital heart disease.

Fanconi [1] first described this syndrome in 1927 in three brothers, each of whom died of an aplastic-type anemia which began, in each case, at the age of 6 years. Microcephaly, generalized brown skin pigmentation, hypoplasia of the testes, and convergent strabismus were also present. Other instances of a familial occurrence of this syndrome have been reported by Emile-Weil [2] (two brothers), Hjorth [3] (brother and sister), and Dacie and Gilpin [4] (two brothers and a first cousin). Rohr [5] has described a similar hematological picture, which probably fits into this group, in two adult brothers—the only reported cases in adults. Sporadic occurrences of this syndrome have been discussed by Uehlinger,[6] van Leeuwen [7] Emile-Weil,[2] Zellweger,[8] Estren, Suess, and Dameshek,[9] and Diamond.[10] The latter stated

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6. Uehlinger, E.: Konstitutionelle infantile (perniciosaartige) Anämie, Klin. Wchnschr. **8**:1501, 1929.

7. van Leeuwen, H. C.: Ein Fall von "konstitutioneller infantiler perniziosaähnlicher Anämie" (Fanconi), Folia haemat. **49**:434, 1933.

8. Zellweger, H., and Zollinger, H. U.: Über einen sporadischen Fall von konstitut, infantiler Panmyelopathie Fanconi: Case, Helvet paediat. acta **1**:382, 1940.

9. Estren, S.; Suess, J. F., and Dameshek, W.: Congenital Hypoplastic Anemia Associated with Multiple Developmental Defects (Fanconi syndrome): Report of a Case, Blood **2**:85, 1947.

10. Diamond, L. K.: Familial Aplastic Anemia with Multiple Congenital Defects (Fanconi's Syndrome), in Textbook of Pediatrics, Philadelphia, ed. 5, W. B. Saunders Company, 1950.

in 1950 that three cases had come to his attention in the past 20 years, though no detailed case histories were given. Although this syndrome was first described in 1927, the only cases occurring in children in the American literature are those reported by Estren, Suess, and Dameshek, in 1947, and by Diamond, in 1950.

We are reporting another instance of this syndrome occurring in an American-born child, which, so far as we can determine, is the third such case in the American literature. In addition to hypoplastic anemia and generalized brown pigmentation of the skin, this patient had microcephaly, mental retardation, microphthalmos, strabismus, hearing deficit, dwarfism, obesity, developed and enlarged breasts (though otherwise sexually immature), and abnormalities of the extremities, with short, broad hands, short, tapering fingers, an abnormality of the right thumb, and partial syndactylism of the second and third toes bilaterally.

REPORT OF CASE

D. G., a white girl of 11 years, was first admitted to the pediatric ward of the University of California Hospital on Jan. 20, 1949, with severe anemia and multiple congenital defects.

Family History.—She was born in California of Italian parentage. There are three siblings, one older and two younger, all living and well. There was no history of occurrence within the family of anemia, congenital defects, tuberculosis, or other significant illnesses. Examination of both parents and of the two younger siblings revealed no splenomegaly, and blood counts, as well as red blood cell fragility, were normal in all.

Past History.—The mother's pregnancy was uncomplicated save for an illness during the second month of gestation, possibly viral in nature, manifested by a severe upper respiratory tract infection and generalized aches and pains. No rash was noted. The patient was born at term after a normal delivery. The weight was 5 lb. 1½ oz. (2,300 gm.). At birth a small head and unusual facial appearance with small eyes were noted. She was breast fed for 18 months. Vitamin supplements were taken regularly throughout infancy but very irregularly thereafter. She had had measles, whooping cough, and chicken pox. She had grown slowly, always being of rather small stature. Early development was not unusual, as she sat alone at 7 months, walked alone at 13 months, and talked at the "usual time." However, by the age of starting school some mental retardation was apparent.

Present Illness.—Save for the congenital defects noted at birth, including her small head and eyes, and her rather slow growth, she was apparently well until the age of 7 years, when she was said to have slight anemia (hemoglobin 12.2 gm. per 100 cc., red blood cells 4,250,000). Since 6 years of age she had complained of vague dull abdominal pains, usually periumbilical in location, which were not associated with meals and were not accompanied with nausea, vomiting, or melena. This abdominal pain had been a recurrent though mild complaint until entry. Barium enema and gastrointestinal series were reported as revealing no abnormalities. Iron, multivitamins, and thyroid orally were given at the age of 7 years. These were taken regularly at first, then sporadically, and were without apparent beneficial effect. By the age of 8½ years an olive tint was noted in the skin, and the anemia had become definite (hemoglobin 8.5 gm., red blood cells 3,340,000). At the age of 10 years, the red blood cell count was 2,720,000 and hemoglobin was 11.3 gm. No jaundice was noted at any time. There had been no evidence of infection, blood loss, or a bleeding tendency. Likewise, there was no history of contact with, or ingestion of, substances known to be toxic to the bone marrow, including sulfonamides and other drugs. Because of increasing pallor and weakness and severe anemia she was admitted to the University of California Hospital.

Physical examination revealed a short, obese girl appearing younger than her 11 years, with extremely pale, nonpigmented mucous membranes and a generalized olive-brown pigmentation of the skin (Fig. 1).

Her measurements were height 124.5 cm. (49 in.), arm span 126 cm. (49.6 in.), head circumference 46.1 cm. (18.1 in.), and chest circumference 70.1 cm. (27.6 in.). Her weight was 34.1 kg. (75 lb.).

The skin, save for the pigmentation mentioned, was clear, there being no petechiae, purpura, or bruises. The head appeared microcephalic. Examination of the eyes revealed bilateral

microphthalmos. The palpebral fissures were narrow and slanted, the outer margin being a little higher than the inner one, and inner epicanthic folds were present. The extraocular muscles were intact; however, an alternating external strabismus was evident. The fundi appeared

Fig. 1.—Photograph of the patient. Note the microcephaly, microphthalmos, and gynecomastia.

Fig. 2.—Appearance of the hands of the patient (left) and of the mother (right) for comparison. Note the increased pigmentation of the patient's skin.

normal. The left tympanic membrane was retracted, and there was evidence of an old hemorrhage in the right middle ear. A conduction-type deafness of the left ear was found (she was unable to hear a tuning fork in the air on the left, although she could on the right). Weber's

TABLE 1.—*Representative Laboratory Data*

Date	Therapy	Hemoglobin, Gm./100 Cc.	Blood Cell Count: Red, × 10^6	Blood Cell Count: White	Neutrophiles, %: Filament	Neutrophiles, %: Nonfilament	Eosinophiles, %	Basophiles, %	Lymphocytes, %	Monocytes, %	Metamyelocytes, %	Myelocytes, %	Other Laboratory Data *
4/19/48	.....	11.0	2.72	.....	..	..	..	..	..	..	..	..	.....
5/10/48	.....	11.3	2.61	.....	..	..	..	..	..	..	..	..	.....
1/20/49	.....	3.5	1.26	3,400	24	2	..	1	72	1	..	..	M.c.v. 103; m.c.h. 28.6; m.c.h.c. 28.7; p.c.v. 13; retic. 26.2%
1/22/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
1/27/49	.....	12.8	3.99	3,250	68	2	..	..	30	..	..	..	.....
2/23/49	.....	3.5	0.93	3,600	26	9	1	..	63	..	..	..	M.c.v. 106; m.c.h. 35; m.c.h.c. 34; p.c.v. 15
2/25/49	.....	....	....	.....	..	..	..	..	..	..	..	..	.....
3/ 1/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	Thromb. 110,000
3/ 2/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
3/ 4/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
3/ 9/49	.....	11.0	3.71	5,400	26	3	1	..	68	..	..	..	.....
3/16/49	.....	8.5	2.88	.....	..	..	..	..	..	..	..	..	.....
3/23/49	....	7.5	2.28	3,600	..	..	..	..	..	..	..	..	.....
4/20/49	.....	< 2.0	0.98	5,700	32	3	1	1	60	3	..	..	.....
4/22/49	Transfusion	0.8	0.65	.....	..	..	..	..	..	..	..	..	Thromb. 210,000
4/23/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
4/28/49	Transfusion; splenectomy	....	....	.....	..	..	..	..	..	..	..	..	.....
4/29/49	.....	12.4	4.0	5,500	..	..	..	..	..	..	..	..	Retic. 1.9%
5/ 3/49	.....	9.4	4.01	2,600	..	..	..	..	..	..	..	..	Thromb. 240,000; retic. 3.1%
5/25/49	.....	7.0	2.35	3,100	9	1	..	..	90	..	..	..	.....
6/ 8/49	.....	6.5	2.13	3,900	6	7	3	..	83	1	..	..	.....
6/22/49	.....	4.0	1.35	.....	..	..	..	..	..	..	..	..	.....
6/27/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
8/ 3/49	.....	2.5	0.78	4,200	6	4	..	..	78	..	8	4	.....
8/ 4/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
8/ 5/49	.....	....	....	.....	..	..	..	..	..	..	..	..	Retic. 0.5%
8/ 6/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
8/ 8/49	.....	12.0	....	.....	..	..	..	..	..	..	..	..	.....
10/19/49	.....	3.5	0.96	4,100	30	4	..	..	65	1	..	..	Retic. 0.1%
11/30/49	.....	3.8	1.24	6,400	23	1	..	..	67	1	16	2	.....
12/ 2/49	.....	....	....	.....	..	..	..	..	..	..	..	..	M.c.v. 96; m.c.h. 29; m.c.h.c. 32; thromb. 250,000; retic. 1.9%
12/ 7/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
12/11/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
12/13/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	Bleeding time 20 min.; clotting time 5 min.; thromb. 100,000
12/14/49	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
12/15/49	.....	14.8	4.2	9,100	..	..	..	..	..	..	..	..	.....
1/25/50	.....	5.0	2.06	13,400	..	8	2	38	..	25	15	12	.....
2/ 9/50	.....	3.5	0.85	19,200	2	53	..	..	25	9	2	..	Thromb. 120,000; retic. 2%; young lymphocytes 9%
2/10/50	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
2/11/50	Transfusion	....	....	.....	..	..	..	..	..	..	..	..	.....
3/ 1/50	.....	8.0	2.92	14,600	6	4	2	..	76	6	..	6	.....
3/17/50	.....	5.4	2.1	8,950	23	12	8	..	40	2	10	5	Beginning 3/17, repeated transfusions for recurrent anemia for next 8 mo.
4/20/50	.....	3.4	1.37	14,250	..	..	..	..	..	..	..	..	.....
5/17/50	.....	7.8	2.72	10,500	9	7	10	1	60	1	12	..	.....
6/20/50	.....	9.5	3.3	47,400	..	..	..	..	..	..	..	..	.....
6/28/50	.....	....	....	28,700	14	13	1	..	31	..	25	16	.....
7/11/50	.....	10.0	3.9	12,900	22	4	6	4	55	7	1	1	Thromb. 90,000; retic. 0.05%; young lymphocytes 1%
8/ 2/50	.....	4.8	1.6	59,000	6	23	3	..	46	2	14	6	.....
9/ 6/50	.....	3.0	1.42	43,200	..	..	..	..	..	..	..	..	.....
9/15/50	.....	3.0	1.5	16,200	..	..	..	..	..	..	..	..	.....
10/ 4/50	.....	6.0	1.92	19,000	3	43	..	..	40	..	10	4	.....
10/ 8/50	.....	4.0	1.8	23,000	15	8	4	5	45	2	16	3	.....
10/24/50	.....	12.0	4.0	14,200	..	..	..	..	..	..	..	..	.....
11/15/50	.....	10.0	2.68	23,800	..	..	..	..	..	..	..	..	.....
11/24/50	.....	8.0	2.55	29,000	..	..	..	..	..	..	..	..	.....

* M.c.v. indicates mean corpuscular volume, cubic microns; m.c.h., mean corpuscular hemoglobin, micromicrograms; m.c.h.c., mean corpuscular hemoglobin concentration, %; p.c.v., packed cell volume, %; thromb., thrombocytes; retic., reticulocytes.

test revealed lateralization of bone conduction to the left. The nose, mouth, and pharynx were clear. The palate was high. The lymph nodes were not significantly enlarged. The neck appeared very short. Her breasts were enlarged and developed out of proportion to the rest of her physical development. The heart was not enlarged, and no murmur was heard. The blood pressure in the arm was 96 systolic, 64 diastolic. The abdomen was very obese. The liver and spleen could not be palpated. The external genitalia were those of a normal immature girl: no pubic hair was present. Abnormalities of the extremities included short and broad hands and short and tapering fingers; the interphalangeal joint of the right thumb was practically immobile, and there was slight syndactylism of the second and third toes bilaterally. No neurological abnormalities were detected.

Laboratory Examination.—The blood count on entry showed hemoglobin level 3.5 gm., red blood cell count 1,260,000, white blood cell count 3,400, packed cell volume 13% (Table 1). The

TABLE 2.—*Sternal Bone Marrow Counts*

	1/22/49	2/28/49	12/2/49	2/11/50
Myeloblasts, %	...	0.5	0.4	2.0
Promyelocytes, %	...	...	7.2	2.0
Myelocytes, %				
Neutrophile	2.3	2.5	6.4	7.0
Eosinophile	...	...	0.8	1.5
Basophile	...	...	...	...
Metamyelocytes, %				
Neutrophile	1.0	6.5	5.2	9.0
Eosinophile	...	...	...	0.5
Basophilic	...	...	...	...
Polymorphonuclear leucocytes, %				
Neutrophile, nonfilament	5.0	5.0	22.6	11.0
Neutrophile, filament	3.0	4.0	2.2	7.0
Eosinophile	...	0.5	1.2	3.0
Basophile	...	...	0.4	1.0
Lymphoblasts, %	...	...	...	0.5
Early lymphocytes, %	...	1.0	3.0	2.5
Lymphocytes, %	18.6	16.5	32.6	20.0
Plasma cells, %	...	...	2.0	...
Monoblasts, %	...	...	...	...
Early monocytes, %	...	...	0.4	...
Monocytes, %	...	0.5	3.2	12.5
Megaloblasts, %	...	2.0	...	...
Proerythroblasts, %	...	...	0.2	...
Erythroblasts, %	11.0	6.5	4.4	0.0
Normoblasts, %	56.6	55.0	6.0	1.5
Reticulocytes, %	...	...	1.9	...
Megakaryocytes	Diminished			

differential count showed 26% neutrophiles, 1% basophiles, 72% lymphocytes, and 1% monocytes. There was a marked reduction in the number of thrombocytes (platelets) seen on the smear, and some anisocytosis and poikilocytosis of the red cells was noted. Wintrobe indices revealed a macrocytic, hypochromic anemia. Subsequent determinations showed the same type of blood picture. The bleeding time was 3½ minutes, clotting time 2 minutes. The clot retraction was poor. The thrombocyte count was 170,000 (normal 350,000 to 550,000), the reticulocyte count 26.2%. The red cell fragility was within normal limits, hemolysis beginning in 0.40% and complete in 0.25% solution of isotonic sodium chloride, as compared with a control beginning at 0.40% and complete at 0.30% (finger-blood method). Several preparations for red cell sickling gave negative results. No autoagglutinins or hemolysins could be demonstrated in the blood. The icteric index was 15 units. The blood type was group A, Rh positive. Repeat urinalyses were negative, including tests for the presence of bile or hemoglobin. A 72-hour stool specimen, weighing 240 gm., contained 96 mg. of urobilinogen, which was within normal limits. The stool was negative for occult blood. The sternal bone marrow was somewhat hypocellular but revealed a marked preponderance of the erythroid elements, there being 56.6% normoblasts and 11.0% erythroblasts in the differential count. Only 11.3% of the cells were of the myelogenous series. Virtually no megakaryocytes were seen (Table 2). Wassermann and tuberculin skin reactions

were negative. Roentgenographic examination of the hands, wrists, chest, spine, and skull revealed no bone abnormalities, save for the skull, which was smaller in all dimensions than usual. Psychometric evaluation gave an I. Q. of 70.

Course of Disease.—Treatment included several whole-blood transfusions, which increased the hemoglobin to 12.8 gm., and red blood cell count to 3,990,000, and resulted in marked symptomatic improvement. The patient was discharged on a therapy of ferrous sulfate, 200 mg. three times daily.

However, the anemia recurred, which necessitated readmission one month later, Feb. 23. Again she had marked pallor, weakness, and some dyspnea. The only evidence of blood loss or of a bleeding tendency during the interval was a severe epistaxis just prior to readmission. Hemoglobin then was 3.5 gm., with a red blood cell count of 930,000; leucopenia (5,100), relative lymphocytosis (63%), and thrombopenia (110,000) again were observed. The bone marrow was essentially unchanged. The icteric index was 9 units. She was again transfused with a total of 1,000 cc. of whole blood, which raised the hemoglobin to 11 gm., the red blood cells to 3,710,000, and resulted in symptomatic improvement.

Despite adequate diet and supplementary vitamins and iron, the anemia recurred, which necessitated readmission to the hospital two months later, April 22, at which time pancytopenia again was found—the hemoglobin being 0.83 gm., the red blood cell count 650,000. The reticulocyte count was 1.9%. Other laboratory examinations showed a phenolsulfonphthalein renal-function reaction normal (65% excretion in 30 minutes, 80% in 90 minutes), nonprotein nitrogen 45 mg. per 100 cc., serum cholesterol 234 mg. per 100 cc., and blood hormonal iodine 5.0 γ (normal 4.0 to 8.0 γ). Intravenous pyelograms revealed no renal abnormalities.

Although it was felt that the principal hematological difficulty in this case was pancytopenia secondary to congenital hypoplastic marrow, the possibility that the spleen might be exerting an inhibitory effect upon the marrow was considered. Consequently, after the anemia was again corrected by transfusion, a splenectomy was performed, on April 28. A normal-sized spleen, weighing 95 gm., was removed. Microscopic examination of the spleen revealed the capsule and trabeculae to be normal. The lymphoid follicles were normal in number and distribution. The germinal centers of many of the follicles showed small deposits of hyalinized eosinophilic material. Greatly increased phagocytosis, with deposition of golden-brown pigment in the macrophages within the sinusoids and red pulp, and reticuloendothelial hyperplasia were noted. There was no evidence of extramedullary hematopoiesis. At the time of splenectomy an intra-abdominal exploration was carried out. The uterus was found to be a very tiny organ but otherwise not abnormal; both ovaries were normal in position and size. No other abnormalities were found. The patient recovered from this operation without complications. There was no significant rise in thrombocyte count after splenectomy.

Splenectomy, unfortunately, had no apparent beneficial effect—the refractory anemia continuing to progress, with the rate of loss of hemoglobin being approximately the same as before splenectomy, and repeated hospitalization for whole-blood transfusions were necessary at progressively shorter intervals.

She was admitted for a sixth time in November, 1949, and during this hospital stay the sternal bone marrow was reexamined and revealed a considerable change from before, it now being more definitely hypocellular, with a marked reduction of cells of the erythroid series to 10.6% (Table 1). The reticulocyte count was 1.9%. Further clinical evidence of a bleeding tendency occurred during this entry; there were slight bleeding from the gums, a few purpuric spots on the mucous membrane of the palate and pharynx, and an ecchymosis on the forearm. The bleeding time was 20 minutes and the thrombocyte count 100,000. The latter remained consistently low. It is interesting that the white cell count became elevated above 6,000 (Table 1) for the first time during this entry, seven months after splenectomy. Immature white cells also appeared in the peripheral blood at that time and were related to the rather frequent secondary infections of the face, cervical nodes, and lungs which she had begun to have.

Another bone marrow examination, in February, 1950, revealed no significant shift towards immaturity of the white cells; however, a further marked reduction in cells of the erythroid series was noted, only 1.5% of the cells being normoblasts, and no younger red cells were seen. Along with this progressive diminution of red cell production by the marrow, the reticulocyte count was lower, in January, 1950, having been only 0.02%. This rose to 2% in February, but in March it again had dropped to very low levels.

In January the white cell count for the first time rose above 10,000. At this time it was noted that she had a disseminated infiltrative process throughout both lung fields. She was given penicillin, with subjective and clinical improvement; but the infiltrative process visualized by roentgen examination continued to be present. Funduscopic examination on March 1 revealed scattered hemorrhages in the fundus of both eyes, some with rather pale centers.

In May an infection of the left side of the face developed which started as a pimple on the left side of the nose. The infection spread and was associated with sufficient edema to cause the eye to be swollen shut. With the administration of penicillin, this infection cleared. In June she had a swelling and infection of the right side of the face. On reentry to the hospital she was found to have right cervical adenitis which was very tender but nonfluctuant. Wheezes, rales, and rhonchi were heard throughout both lung fields, and there was dulness of the right side of the chest posteriorly. The breath sounds were decreased in this area, and crepitant rales with superimposed, generalized, coarse, sibilant wheezes were noted. Administration of penicillin (penicillin S-R.®), 400,000 units a day, was started, and after two days it was increased to 400,000 units twice a day. The white cell count at this time was 47,400. A hemolytic Staphylococcus aureus, which was later found to be resistant to penicillin, was cultured from the nose. Since the clinical response to penicillin was poor, she was given terramycin on the fifth hospital day, 500 mg. every six hours, and use of penicillin was discontinued. The cervical mass localized and spontaneously began to drain. While the patient was receiving terramycin, a very hemolytic Staph. aureus from the nose and throat grew on culture, and the white blood cell count persistently remained above 20,000 during the entire hospital stay.

On Aug. 2, 1950, she reentered the hospital with pneumonia. She was given penicillin and terramycin, but, because of a lack of improvement, penicillin was increased to 1,000,000 units every two hours. Two days after entry digitoxin administration was started because of signs of congestive failure. A pure culture of hemolytic Staph. aureus was grown from sputum, and this organism, which previously had been very sensitive to terramycin, was now found to be insensitive to penicillin, terramycin, and aureomycin, although it was sensitive to chloramphenicol (chloromycetin®). Therefore, the penicillin and terramycin were withdrawn, and chloramphenicol was instituted as the therapeutic drug. During her hospital stay she had two episodes of epistaxis. A roentgenogram of the chest still showed widespread pneumonitis, and eventually a radiolucent area in the superior segment of the lower lobe on the left, which had a straight inferior border representing an air-fluid level, appeared. This was an abscess which had apparently excavated into a bronchus. In spite of the persistence of positive cultures of the nose and throat for hemolytic Staph. aureus, clinical improvement was good, and the white blood cell count dropped from 59,000 on entry to 5,450 before discharge.

On Aug. 26 she reentered the hospital; the hemoglobin was found to be down to 3 gm., red blood cell count to 1,420,000, and white blood cell count to 43,200. There was hemorrhage from the genitourinary tract, and there were numerous petechial hemorrhages over the entire body and on the mucous membranes. Toluidine blue was given in an attempt to alleviate some of the bleeding, but without any marked immediate change in her condition. After transfusion she showed a gradual improvement.

For the next three months she continued to have frequent hospital entries for rapidly progressive anemia and flare-ups of her infective processes, including an abscess of the buttock. A transfusion was given on Oct. 10, and shortly thereafter she seemed to feel better than she had for several months previously. During this period the drop in hemoglobin was also slower than it had been at an earlier time, but a flare-up of the pulmonary infection occurred late in November, and her final hospital entry was on Nov. 24, 1950, when she appeared to be moribund and had widespread evidence of pulmonary infection and signs of cardiac decompensation. Again chloramphenicol and digitoxin were given, but she had a progressively downhill course and died on the fourth hospital day.

GROSS EXAMINATION AT AUTOPSY

General Examination.—The body was well developed and well nourished. Around the neck and in the axillae the skin was a much darker brown color than elsewhere. Minute pinpoint white spots were scattered uniformly over the darkened surfaces. The increased pigmentation

was seen to a less extent in the antecubital fossae, the inguinal regions, over the lower abdomen, and over the skin surfaces of the labia majora. The texture of the skin remained unchanged in the pigmented areas. A small amount of purulent material could be expressed from abscesses of the buttocks. Striae of both breasts and over both upper thighs were present. There were very sparse, fine, blonde, short hairs on the external genitalia. The head had normal contours, measuring 42.5 cm. in circumference. The buccal and gingival mucosa were pale and showed no pigmentation. The breasts showed marked early development, and firm breast tissue was palpated on both sides. The genitalia appeared underdeveloped. The fingers were short and showed slight "spindle" configuration. Syndactylism of the second and third toes of both feet was present.

Chest.—There was no free fluid in the pleural cavities. The bases of both lungs were adherent to the upper surface of the diaphragm. The trachea contained large amounts of thick purulent material. The thymus was markedly involuted, and only a few soft, flat strands of dark-yellow tissue appeared to represent the remains of the gland. The lymph nodes in the superior middle mediastinum were soft, dark yellow, and moderately prominent. These nodes continued inferiorly with enlarged hilar lymph nodes and superiorly with the large cervical nodes on both sides of the neck.

Heart.—The heart weighed 170 gm. There was an increase in epicardial fat, and all chambers appeared moderately dilated and the walls thickened. Scattered throughout the myocardium were small bright-pink hemorrhages measuring up to 0.5 cm. in diameter.

Lungs.—The pleura was thickened at the bases. A nodular mass was palpated in the upper portion of the lower lobe of the left lung. Sections throughout revealed dark-red nodular areas everywhere, and in the upper portion of the lower lobe of the left lung an empty thick-walled cavity approximately 1.5 cm. in diameter was found. Large amounts of thick purulent material filled the larger bronchial passageways. The same substances could be expressed from the smaller units by compression of the lung tissue. The hilar lymph nodes were markedly enlarged and moderately anthracotic.

Abdomen.—Fibrous adhesions of moderate firmness attached loops of small bowel against the abdominal wall in the left upper quadrant. The mesenteric lymph nodes were not prominent. A few minute calcified foci were found on the floor of the peritoneum.

Liver.—The liver weighed 1,250 gm. and had the normal configuration. The capsule was smooth, glistening, and not thickened. Cut section revealed a firm, light-reddish-brown cut surface in which minute, poorly defined, dark-yellow areas were interspersed.

Genitalia.—The uterus and tubes did not appear unusual. The ovaries each measured 0.7 cm. in their greatest diameters and were smooth and light yellow.

Bone Marrow.—The marrow everywhere was dark reddish brown and moist. The bony trabeculae were not prominent.

Central Nervous System.—The brain weighed 840 gm. The gyri appeared slightly atrophic.

MICROSCOPIC EXAMINATION AT AUTOPSY

Brown, finely granular pigment which stained for iron was found in (1) almost all the cardiac muscle cells, usually perinuclear in position; (2) the vascular area at the surface of the lungs, where it was scattered diffusely, extracellularly, or in compactly filled phagocytic cells; (3) the alveolar walls and contents; (4) the peribronchial region; (5) the liver cells, Kupffer cells, sinusoids, and lymphatics of the liver; (6) the acinar, islet, and small-duct epithelial cells of the pancreas; (7) Brunner's glands and interstitial tissue in the villi stalks of the small intestine; (8) the zona glomerulosa cells of the adrenals; (9) the loops of Henle of the kidney; (10) the bone marrow, and (11) the epithelial lining cells of the choroid plexus.

Lungs.—At the surface of the lower lobe of the left lung there was a shaggy thickening exterior to the pleura consisting of multiple engorged, thin-walled blood vessels. There was little supporting stroma to these vessels, and the stroma consisted of very fine collagenous fibers. The alveolar lining cells were made out with difficulty. Around bronchioles and bronchi were dense infiltrations of lymphocytes, a few plasma cells, small and large mononuclear cells; the latter sometimes resembled immature forms of myelocytes. The solid portions of lung which

were seen grossly were composed of compact areas of cellular infiltrate similar to that around the bronchi, described above. In addition, the alveoli were filled with dense masses of polymorphonuclear leucocytes, many of them relatively young forms. Serous, fibrinous, and blood materials also were present in the alveoli. The bronchial epithelium in many places was destroyed or metaplastic. The connective tissue of the peribronchial region was increased, sometimes to a marked extent, and inflammatory cells were scattered throughout. The abscess cavity was lined by a narrow layer of fine reticular fibers and small spindle-shaped cells. Beneath the lining were various types of cells, including iron-pigment-filled cells, plasma cells, lymphocytes, rare polymorphonuclear cells, giant cells, and large mononuclear cells, admixed with fibrinous trabeculae and many small, engorged capillaries. Very dense, thick collagenous layers were lying next to the alveolar tissue.

Liver.—The capsule appeared slightly thickened. In lymphatics beneath the capsule and in the portal area were diffuse aggregates of small, dark cells. Most of the cells were lymphocytes, plasma cells, and small mononuclear cells. Frequent polymorphonuclear leucocytes and eosinophiles were seen.

Adrenals.—The zona fasciculata cells were necrotic. The rest of the cortical cells were large, densely or lightly pink, and appeared larger than usual. They contained little or no lipid substances. The medulla did not appear remarkable.

Kidneys.—Principal changes in this organ were in the tubular system. In some instances the pigmented epithelium of the loops of Henle had sloughed off into the lumen and undergone calcification. Pronounced hydropic degeneration was found in the proximal convoluted tubules. The glomeruli appeared slightly avascular. Almost all tubules showed basal fatty epithelial changes.

Genitalia.—Many primordial follicles containing primitive oocytes were found in the ovary, none of which showed signs of development. The tubal and uterine epithelium were of the simple type associated with immaturity.

Breast.—There were a few simple ducts embedded in a dense hyalin-abundant stroma. No acini were seen.

Lymph Nodes.—Almost all the nodes were similar in appearance. Clusters of deeply iron-pigmented reticuloendothelial cells were seen, principally in the peripheral sinuses. The usual architecture was destroyed, and cellular population appeared reduced in number. The cells which were present appeared to be large, immature, hematopoietic cells, some of which were in mitosis. Mature forms were not evident except for a few adult lymphocytes.

Skin.—The epidermis was thin and atrophic. A hyperkeratotic layer overlaid the surface. The skin showed moderate pigmentation of the basal layer. No iron was present. There was very slight perivascular leucocytic infiltration.

Bone Marrow.—The marrow was packed with numerous large nucleated cells predominantly of the immature myelocyte series. Plasma cells and lymphocytes were present, but very few mature red blood cells, and even fewer of the immature forms, were seen. Megakaryocytes were markedly decreased in number. Many iron-pigment-filled reticuloendothelial cells were scattered diffusely everywhere. Eosinophiles were moderately prominent.

Central Nervous System.—In the cortex there was increased gliosis, and some of the glial cells were associated with neurons showing degenerative changes. The nerve cells themselves showed disorientation, and there was loss of the usual distinctive layering of cells. The capillary structures were unusually prominent, and there was minimal leakage through some of the walls. The internal granular layer of the cerebellum showed marked depletion of the cellular elements.

Pathologic Diagnoses.—The pathologic diagnoses were the following: (1) hypoplasia of red cell elements and thrombocytes in bone marrow; (2) leukemoid reaction of lymph nodes, bone marrow, and liver; (3) severe bronchopneumonia; (4) abscess of lower lobe of left lung; (5) petechiae of myocardium and bladder; (6) hemochromatoses with minimal hepatic (portal) and pancreatic fibrosis and iron-pigment deposition in cells of multiple organs; (7) acute esophagitis; (8) gluteal abscess; (9) syndactylism of second and third toes bilaterally; (10) microcephaly, and (11) chronic anoxia of cerebral tissues.

COMMENT

The occurrence of severe progressive refractory macrocytic anemia with pancytopenia in association with an olive-brown pigmentation of the skin and other congenital defects, and called the Fanconi syndrome by several authors, warrants the addition of this case to the group originally described by Fanconi. Our patient showed the following defects:

1. Skeletal system: Short stature had always been noted. The hands were short and broad, with short and tapering fingers. The interphalangeal joint of the right thumb was practically immobile, and there was slight syndactylism of the second and third toes bilaterally. However, roentgenograms of the extremities did not reveal any abnormality.

2. Central nervous system: The head was unusually small, and the intelligence quotient was only 70. Although early development was reported as not being unusual, mental retardation was apparent by the age of starting school. An alternating external strabismus was present, and deafness of the left ear was found.

3. Eyes: There was bilateral microphthalmos. The palpebral fissures were narrow and slanted, and inner epicanthic folds were present.

4. Skin: A generalized olive-brown pigmentation of the skin was apparent even before transfusions had been administered. It did not involve the mucous membranes.

5. Endocrine system: The breasts were enlarged and developed out of proportion to the rest of her physical development, and although she was closely followed for almost two years, no other signs of sexual maturation became evident.

6. Hematopoietic system: When first observed, she had panhematopenia, but with good erythroid activity of the bone marrow and an elevated reticulocyte count of the peripheral blood. The marrow gradually became more hypoplastic, and there was an accompanying decrease in the reticulocyte count. However, with the onset of severe staphylococcic infections in the 10 months before she died, leucocytosis and a marked shift to the left of the neutrophiles were noted.

The reported familial incidence of this group of anomalies suggests that at times they may be the result of a familial inheritable trait. Sporadic cases probably represent spontaneous or chance mutations. The defects present in our sporadic case may very well have been the result of injury to the fetus by a viral infection occurring during the second month of the pregnancy. Estren, Suess, and Dameshek reported that the mother of their patient had had otitis and mastoiditis during the third month of pregnancy; and in their case, too, damage to the fetus may have occurred.

The pathogenesis of the hematological changes observed is not entirely clear. The hypoplastic marrow and pancytopenia are similar to those found in aplastic anemia. However, the elevated reticulocyte count seen early in many cases of the Fanconi syndrome, and the marked anisocytosis and poikilocytosis which have usually been noted, differ from the normal-appearing red cells and decreased reticulocyte count usually seen in cases of aplastic anemia of either the primary idiopathic or the secondary type.

Serial bone marrow examinations suggest that the inability of the marrow to produce red cells is progressive in nature. This is also substantiated by the concomitant reduction in the number of reticulocytes in the peripheral blood.

The elevated reticulocyte count, a marrow very actively producing red cells, and the slightly elevated icteric index found when we first studied this girl all suggested the possibility of a red-cell-destructive or hemolytic factor being present.

We were unable to demonstrate any definite evidence of hemolysis, no auto-agglutinins or hemolysins being demonstrable, and the red cell fragility being normal. Also no increased excretion of urobilinogen in the stool or urine was found.

It has been demonstrated that small islands or areas of active marrow may sometimes be present in a marrow which is for the most part hypoplastic.[11] Therefore, it is possible that our original bone marrow aspirations, at a time when reticulocytosis was present, may have been through such an active area, the reticulocytosis being a manifestation of this small area of activity. Unfortunately, attempts at obtaining bone marrow simultaneously from other sites (tibia and iliac crest) were unsuccessful.

The findings of increased phagocytosis, deposition of a golden-brown pigment in the macrophages, and reticuloendothelial hyperplasia in the spleen removed in our case, along with similar findings which have been observed in other cases of the Fanconi syndrome upon pathologic examination of removed spleens or at autopsy, particularly in the cases of Dacie and Gilpin, and also in that of Estren, Suess, and Dameshek, are of considerable interest. It is possible that at least some of these changes in the spleen are secondary to multiple transfusions, this patient having had a total of seven transfusions, of 500 cc. each, prior to splenectomy. However, it is striking that pigmentation of the skin is considerably more marked in these patients than in others receiving repeated tranfusions, and it was present in our patient before any transfusions had been given. Rohr described the finding of numerous macrophages containing hemosiderin in sections of the skin, spleen, and bone marrow and also a marked reticular, plasmocytic, and tissue mast cell invasion of the bone marrow in his cases, and he suggested that these are the result of pathologic functioning of the reticuloendothelial system. Similar changes occurred in our patient.

Repeated whole-blood transfusions proved to be the only effective means of therapy in our case, but were only of temporary value, and splenectomy was without apparent benefit. There are three reported instances of splenectomy in children with the Fanconi syndrome. Splenectomy did not alter the course of the disease in van Leeuwen's case,[7] the patient dying three years later. In Dacie and Gilpin's case [4] a remission lasting at least three years followed splenectomy. This could not be definitely attributed to splenectomy, however, as the patient had had previous remissions and had required no transfusions for five years prior to splenectomy. In the case of Estren, Suess, and Dameshek there was a definite reduction in the number of transfusions required, although the thrombocyte count did not become significantly elevated. One of Rohr's adult patients was markedly improved after splenectomy. Estren and Dameshek have postulated that the normal spleen exerts an inhibitory or regulatory effect upon the bone marrow. They feel that the occasional benefit seen in hypoplastic anemia of childhood following splenectomy is probably due to removal of this inhibitory mechanism. They point out that it is most likely to be of benefit in persons whose marrow still reveals some evidence of active regenerative ability, particularly patients showing a marked bleeding tendency because of thrombopenia, yet in whom megakaryocytes are still present in the marrow.

Of particular interest in our case was the development of leucocytosis and a marked shift to the left of the neutrophiles under the stimulus of staphylococcic infections of the face, buttocks, cervical nodes (with abscess formation), and lungs

11. Estren, S., and Dameshek, W.: Familial Hypoplastic Anemia of Childhood: Report of Eight Cases in Two Families with Beneficial Effect of Splenectomy in One Case, Am. J. Dis. Child. **73**:671 (June) 1947.

(with abscess formation). Although splenectomy had been performed in the hope that a possible inhibitory effect upon the bone marrow might be removed, the procedure had an unappreciable effect on the white blood cell count. However, when persistent infection developed, the white cell count rose to 47,400 and remained elevated to abnormal heights for most of the remaining six months of the patient's life.

SUMMARY

A case of Fanconi's syndrome (multiple congenital anomalies with hypoplastic anemia) is presented. The patient had anemia, thrombopenia, congenital abnormalites of the skeletal system, microcephaly, microphthalmos, a generalized olive-brown pigmentation of the skin, and breasts enlarged and developed out of proportion with the rest of the physical development. Of particular interest was the occurrence of leucocytosis under the stimulus of multiple staphylococcic infections.

GAMMA GLOBULIN STUDIES IN TUBERCULOSIS IN CHILDREN

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MARKED changes may occur in the blood proteins in many diseases; these changes have long been noted in tuberculosis. Adler,[1] in 1925, found an increase in the globulin fraction in pulmonary tuberculosis related to the severity of the tuberculous process. Luthy [2] studied the serum proteins in tuberculosis in 1927 and found that at first there were normal protein values, but as the process extended these were increased, and during the final stages of the disease there was a decrease to subnormal values. When the albumin-globulin quotient was considered, this was found to be of much greater significance: increasing globulin content seemed to indicate increasing severity of the pathologic process.

Olivier,[3] in 1931, considered the proteins as buffers and changes in protein level as representing attempts to maintain the pH. Normal protein values were found in mild cases, an increase in severe cases or aggravation, and a decrease in cachectic forms of tuberculosis. The albumin-globulin ratio was decreased in active and increased in fibrinous forms, but it was not characteristic for intermediary forms. Sato,[4] in 1933, concluded that the relative globulin value increases with the expansion of the focus and the intensification of the inflammation.

It is now known, however, that there are at least three distinctly different globulins in the serum, and the relative amounts of these vary considerably in disease. Antibodies for most diseases, including tuberculosis, have been found in the gamma globulin fraction.[5] Seibert,[6] making electrophoretic studies of the serum proteins,

From the Children's Division, Cook County Hospital, the Chicago Medical School, and the Hektoen Institute for Medical Research.

1. Adler, A., and Zaruski, M.: Serum Proteins in Tuberculosis, Schweiz. med. Wchnschr. **55**:709, 1925.

2. Luthy, F.: Clinical Studies of Serum Protein Bodies in Pulmonary Tuberculosis, Schweiz. med. Wchnschr. **57**:993, 1927.

3. Olivier, H. R., and Sliosberg, A.: A Study of the Serum Proteins in the Course of Pulmonary Tuberculosis, Rev. tuberc. **12**:5, 1931.

4. Sato, I.: The Serum Proteins in Pulmonary Tuberculosis, Tohoku J. Exper. Med. **22**:116, 1933.

5. Enders, J. F.: The Concentration of Certain Antibodies in Globulin Fractions Derived from Human Blood Plasma, J. Clin. Invest. **23**:510, 1944.

6. (*a*) Seibert, F. B., and Nelson, J. W.: Electrophoretic Study of the Blood Protein Response in Tuberculosis, J. Biol. Chem. **143**:29, 1942; (*b*) Electrophoresis of Serum, Am. Review Tuberc. **47**:66, 1943.

found a statistically significant rise in the gamma globulin of the serum in minimal active tuberculosis, with a corresponding decrease in albumin. Elevations in the gamma globulin have also been found in many other diseases, including multiple myeloma,[7] carcinoma,[6b] sarcoid,[8] and liver disease,[9] and it is believed the gamma globulin is a product of the reticuloendothelial system and represents the result of reticuloendothelial stimulation.

PRESENT STUDY

De la Huerga and associates[10] recently described a turbidimetric method of determining gamma globulin, corresponding very closely to the more complex electrophoretic determinations.[11] Using this quick method, 73 children with various types of tuberculosis were studied from three to eight months, with weekly determinations of their serum gamma globulin, to determine whether or not the levels followed any particular pattern during the course of tuberculosis. Sedimentation rates (Wintrobe), hematocrit readings, and total and differential white cell counts were run concurrently to see what relationships, if any, there are among these laboratory tests in the disease.

The upper limit of normal for serum gamma globulin is recognized as 1.30 gm. per 100 cc. in adults.[10] Knapp and Routh[12] showed that the gamma globulin

TABLE 1.—*Gamma Globulin Levels in Relation to Sex and Race*

Sex and Race	Number of Cases	Average High Gamma Globulin Level, Gm./100 Cc.
Male Negro	21	1.48
Female Negro	36	1.50
Male white	9	1.46
Female white	7	1.36

decreased from unusually high values in the newborn to unusually low values in infancy, then gradually increased with age to reach the normal adult level in mid-childhood, 5 to 11 years of age. They and other authors[13] found levels of gamma globulin to be uniformly below 0.5 gm. per 100 cc. in normal infants beyond the newborn period but below one year of age and below 1.0 gm. per 100 cc. in normal

7. Kekwick, R. A.: The Serum Proteins in Multiple Myelomatosis, Biochem. J. **34**:1248, 1940.

8. Fisher, A. M., and Davis, B. D.: The Serum Proteins in Sarcoid: Electrophoretic Studies, Bull. Johns Hopkins Hosp. **71**:364, 1942.

9. Popper, H.; de la Huerga, J.; Steigman, F., and Slodki, M.: Turbidimetric Gamma Globulin Determinations in Hepatobiliary Diseases, J. Lab. & Clin. Med. **35**:391, 1950.

10. de la Huerga, J., and Popper, H.: Estimation of Serum Gamma Globulin Concentration by Turbidimetry, J. Lab. & Clin. Med. **35**:459, 1950.

11. de la Huerga, J.; Popper, H.; Franklin, M., and Routh, J. I.: Comparison of Results of Gamma Globulin and Zinc Sulfate Turbidity Tests with Electrophoretic Determination of Gamma Globulins, J. Lab. & Clin. Med. **35**:466, 1950.

12. Knapp, E. L., and Routh, J. I.: Electrophoretic Studies of Plasma Proteins in Normal Children, Pediatrics **4**:508, 1949.

13. Lubschez, R.: Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever: Electrophoretic Patterns in Blood Plasma and Serum in Normal Children, Pediatrics **2**:570, 1948.

children 1 to 4 years of age. These figures were accepted and used by us as the upper limit of normal values for the different age groups.

Chart 1 shows the minimum and maximum values of serum gamma globulin obtained in each of the 73 patients during the study and is broken down to show the type of tuberculosis, the age grouping, and whether or not the patient was treated with streptomycin. The average of the highest levels reached in each of the 73 cases was 1.47 gm. per 100 cc., which is distinctly above the upper limit of normal for adults (1.3 gm.).

In the entire series of 73 patients, 43 were girls and 39 were boys; there were 57 Negro and 16 white children. The breakdown for high gamma globulin reached in relation to sex and race, without regard to type of disease, is shown in Table 1.

The levels are all approximately the same, the only exception being in the case of white girls, who seem to show a lower maximum level than the other groups. However, the small number of white girls used makes this difference not significant.

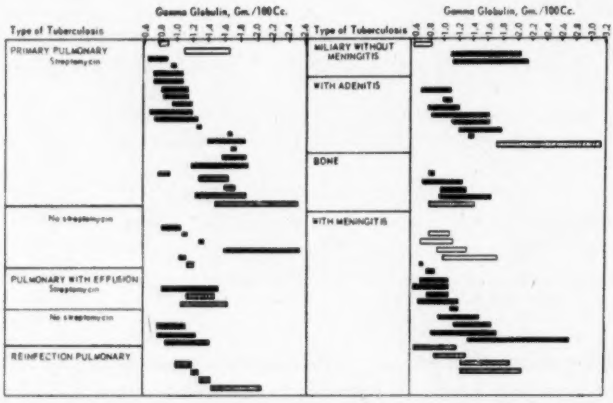

Chart 1.—Minimum and maximum values of gamma globulin obtained in each of 73 patients with various types of tuberculosis during the course of their disease. Patients with primary pulmonary tuberculosis are divided according to whether or not they received streptomycin. Patients with other types of tuberculosis all received some streptomycin. The normal upper limit for gamma globulin for children over 4 years is 1.3 gm. per 100 cc.; 1.0 gm. per 100 cc. represents the upper limit of normal for children under 4 years. Solid white bars indicate children under 1 year; solid black bars, children 1 to 4 years; lined bars, children over 4 years.

TABLE 2.—*Primary Pulmonary Tuberculosis*

Age Group, Yr.	Upper Limit of Normal for Age	Number of Children	Average High Gamma Globulin Level, Gm./100 Cc.
Under 1	0.5	2	1.30
1 to 4	1.0	19	1.44
Over 4	1.3	7	1.61

There was no apparent relation of the gamma globulin level to the hematocrit reading, total white blood cell count, eosinophile count, or monocyte-lymphocyte ratio. There did seem to be an increased monocyte count regularly early in the disease, at the time that the gamma globulin was rising.

TYPES OF CASES

Primary Pulmonary Tuberculosis.—This group comprises 28 cases, and the findings are summarized in Table 2.

Of the 28 patients, 22 were streptomycin-treated. The average high gamma globulin level reached in these 22 patients was 1.43 gm. per 100 cc. The other six patients received no streptomycin; the average high gamma globulin level here was 1.42 gm. per 100 cc. In all age groups the gamma globulin level reached was above the upper limit of normal.

The highest level of gamma globulin in the 28 cases was always reached somewhere between the 3d and 11th weeks from the time of onset of the disease, the

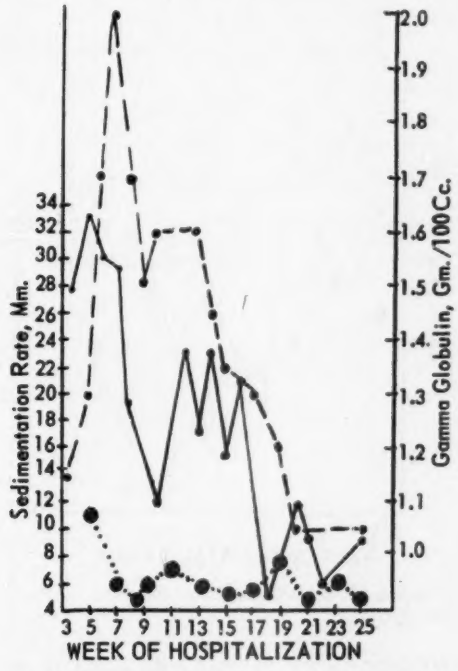

Chart 2.—Course of patient (E. T.) with uncomplicated primary pulmonary tuberculosis who was treated with streptomycin. In Charts 2 through 7, erythrocyte sedimentation rate is indicated by the solid line, gamma globulin by the broken line, and white blood cell count by the dotted line; the total white cell count is the figure at the left × 1,000.

average being at the sixth week. The level usually returned to normal range sometime between the 12th and 26th weeks, but it remained elevated longer than this in four cases. There was no difference in these times between the streptomycin-treated patients and those not streptomycin-treated.

A case typical of this group is shown in Chart 2, which illustrates the early rise in gamma globulin and sedimentation rate, with later parallel decline.

Primary Pulmonary Tuberculosis with Effusion.—This group was made up of six cases (Table 3).

Again there was no significant difference between the streptomycin- and the nonstreptomycin-treated patients. The time of peak gamma globulin was the same as in the uncomplicated primary pulmonary tuberculosis cases. A case typical of this group is shown in Chart 3, and again the chart illustrates high sedimentation rate and gamma globulin, with later decline.

TABLE 3.—*Primary Tuberculosis with Effusion*

Age Group, Yr.	Upper Limit of Normal for Age	Number of Children	Average High Gamma Globulin Level, Gm./100 Cc.
Under 1	0.5	0	....
1 to 4	1.0	4	1.35
Over 4	1.3	2	1.59

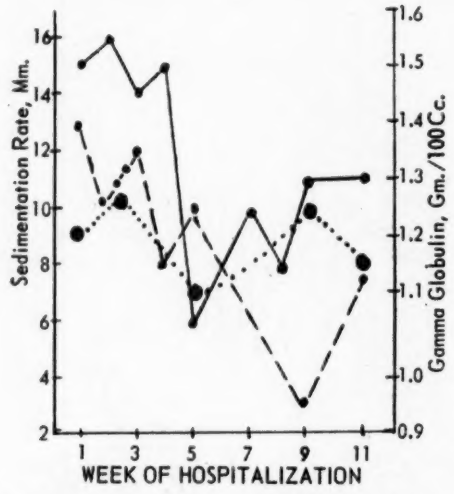

Chart 3.—Course of patient (B. B.) with primary pulmonary tuberculosis with effusion. The patient received no streptomycin.

Reinfection Tuberculosis.—Four patients with this type of tuberculosis were followed, all between 7 and 10 years of age. The average high gamma globulin reached was 1.52 gm. per 100 cc. Two of the patients had high levels about 1.3 gm. per 100 cc., the other two had levels above 1.0 gm. per 100 cc. The gamma globulin remained elevated for somewhat longer periods than in the cases of primary pulmonary tuberculosis. One of these cases is shown in Chart 4; the persistence of elevation of both gamma globulin and sedimentation rate values are shown.

Tuberculous Adenitis.—As seen in Chart 1, there were eight cases in this group with external tuberculous lympadenopathy. Seven patients were between 1 and 4 years of age, and these had an average high gamma globulin of 1.44 gm. per 100 cc., three had levels above 1.3 gm., while the other four had levels above 1.0 gm. The eighth child was above 4 years of age; the high gamma globulin reached was 3.0 gm. per 100 cc.

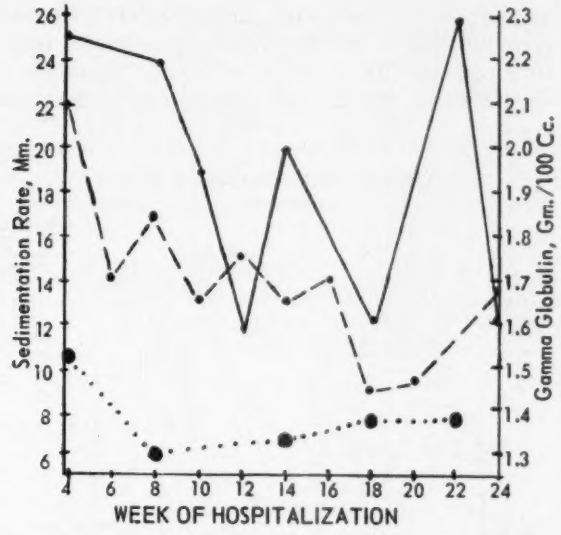

Chart 4.—Course of patient (P. W.) with reinfection of pulmonary tuberculosis. The disease was still active at the time that the last levels were obtained (24th week); at this time the patient was transferred to a tuberculosis sanatorium.

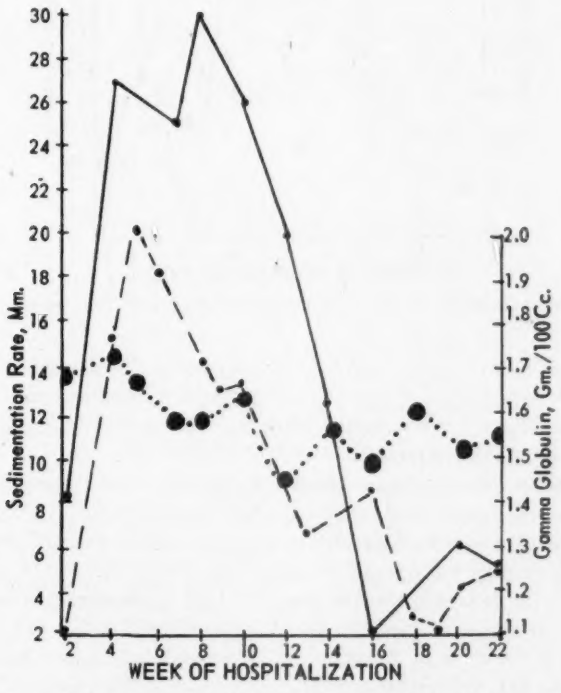

Chart 5.—Course of patient (E. A.) with miliary tuberculosis without meningitis. There is an early rise of gamma globulin and sedimentation rate followed by a later decline.

In these eight cases the abnormally high gamma globulin levels were maintained for much longer periods than in the other types of tuberculosis, these levels being found as long as a year after the onset of the disease. Again, the sedimentation rates also remained elevated. All of these patients received streptomycin at some time in their course.

TABLE 4.—*Tuberculous Meningitis*

Age Group, Yr.	Upper Limit of Normal for Age	Number of Children	Average High Gamma Globulin Level, Gm./100 Cc.
Under 1	0.5	4	1.33
1 to 4	1.0	11	1.37
Over 4	1.3	4	1.57

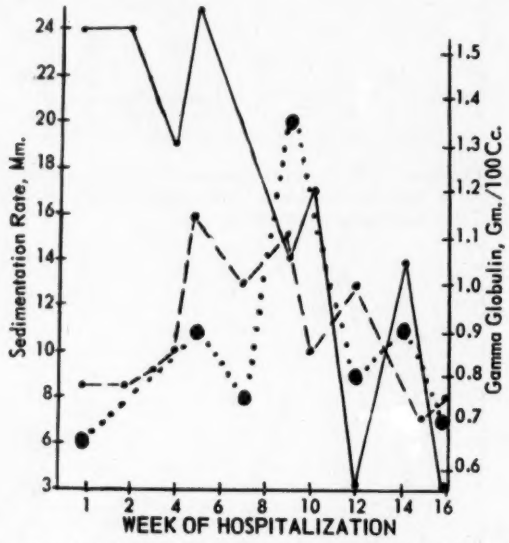

Chart 6.—Course of patient (C. M.) with tuberculous meningitis. This patient was still living at the end of the study.

Bone Tuberculosis.—Five patients in this group were followed. Four of these were between 1 and 4 years of age; the average high reached was only 1.25 gm. per 100 cc. One was over 4 years old and reached a high level of 1.43 gm. All of these patients were streptomycin-treated.

Miliary Tuberculosis Without Meningitis.—There were three patients in this group, all of whom made uneventful recoveries on streptomycin therapy. One was an infant one year of age; the high gamma globulin reached was 0.82 gm. per 100 cc. The other two were between 1 and 4 years of age; their high levels were 2.02 gm. and 2.14 gm., with an average of 2.08 gm. The high levels were reached around the eighth week, and levels returned to normal between the 21st and 26th weeks of the disease. One of the cases in this group is shown in Chart 5, and the early rise of gamma globulin and sedimentation rate, followed by a later decline, is illustrated.

Tuberculous Meningitis.—There were 19 patients in this group, all of whom received streptomycin intramuscularly only (Table 4).

Seven of the 19 patients were still living at the completion of the study; their average high was 1.44 gm. per 100 cc. of gamma globulin. Twelve of the patients died. Their average high reached was 1.38 gm. per 100 cc. This difference is not considered significant. At the time of death, however, the level in the 12 fatal cases ranged from 0.60 to 1.14 gm., the average being 0.90 gm.

Six of these 19 cases developed as complications in cases of primary pulmonary tuberculosis in which treatment with streptomycin was being given at the time of

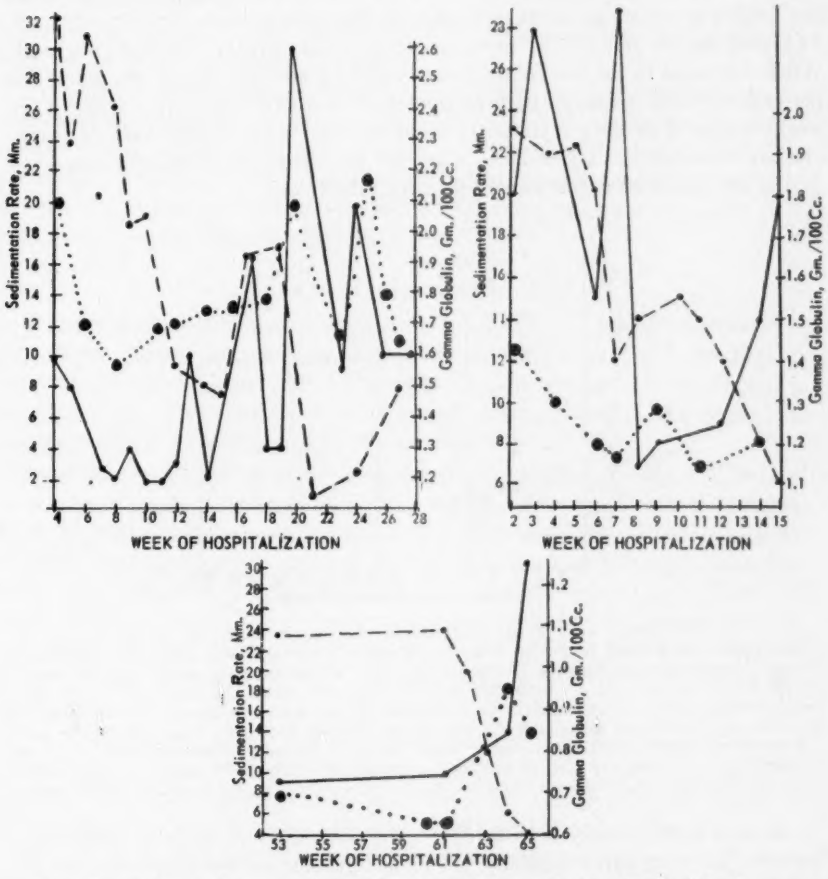

Chart 7.—Courses of three patients with tuberculous meningitis, illustrating the gamma globulin and sedimentation rate dissociation. Left, the first patient (D. H.) had pulmonary tuberculosis with meningitis which developed at the 19th week, at which time the gamma globulin shows a steep fall and the sedimentation rate a steady rise. This patient was alive at the end of the study (28th week). Right, the second patient (C. B.) had primary pulmonary tuberculosis with complicating meningitis at the seventh week; death occurred at the 15th week. There is a gamma globulin and sedimentation rate dissociation at both of these times. Below, the third patient (A. L.) was convalescing from tuberculous meningitis; relapse occurred at the 61st week and death at the 65th week. The gamma globulin fell and the sedimentation rate rose during the period from the 61st to the 65th week.

appearance of the meningitis. Four of the patients died rather soon, while the other two responded to treatment and remained alive.

With regard to the slope of the gamma globulin level in relation to time, there was a steep drop in the gamma globulin level just before the development of the meningitis in the above six cases and in all the fatal ones just before death. This is discussed in greater detail below in relation to the sedimentation rate. Nearly all of these patients had elevated gamma globulin levels early in the course of the disease.

ERYTHROCYTE SEDIMENTATION RATE IN RELATION TO GAMMA GLOBULIN

Maximum erythrocyte sedimentation rate levels were reached between the second and sixth weeks from the onset of the disease, the average being at the fourth week. The levels usually returned to normal somewhere between the 12th and 20th week. When compared to the time of maximum gamma globulin levels, it was found that the gamma globulin reaches its peak a week or two later but stays elevated a few weeks longer than does erythrocyte sedimentation in the typical case of benign primary tuberculosis. The sedimentation rate paralleled the gamma globulin levels during the course of uncomplicated primary tuberculosis.

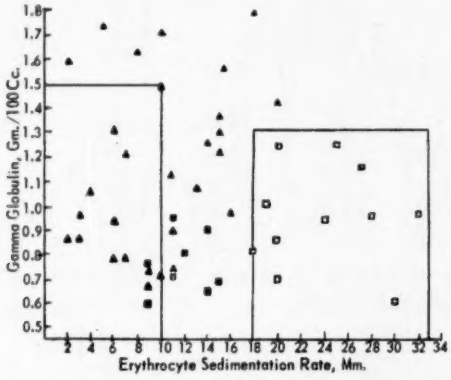

Chart 8.—The lowest level of gamma globulin obtained in each case plotted against the sedimentation rate at that particular time for 28 cases of primary pulmonary tuberculosis and 17 cases of tuberculous meningitis. The rectangle on the left indicates the upper limits of normal for the two tests; no case of meningitis falls into this rectangle. The rectangle on the right includes those cases with extremely high sedimentation rate with low gamma globulin figures: 11 of the 12 cases of fatal meningitis fall into the rectangle at the right, while none of the cases of primary pulmonary tuberculosis appear there. Cases of primary pulmonary tuberculosis are indicated by solid triangles; cases of tuberculous meningitis in which the patient died, by hollow squares, and cases of tuberculous meningitis in which the patient is still living, by solid squares.

In cases ending fatally or with developing complications (such as meningitis), however, there appeared regularly a "gamma-globulin-sedimentation-rate dissociation," with the globulin level falling sharply and the sedimentation rate rising.

From observation, an arbitrary figure of a drop in gamma globulin of at least 0.5 gm. per 100 cc. with a synchronous rise in the sedimentation rate of at least 10 mm. an hour in a two-week period, was used to indicate this dissociation.

This phenomenon never appeared in an uncomplicated case of primary pulmonary tuberculosis. It occurred in one case of reinfection tuberculosis with cavity formation. It occurred in five of the six cases of primary pulmonary tuberculosis in which tuberculous meningitis developed, at one to three weeks before the appearance of the meningitis. It occurred in one case of chronic tuberculous adenitis with

draining sinuses in which there were remissions and exacerbations over a period of years. Finally, this gamma-globulin-sedimentation-rate dissociation appeared in eight of the 12 cases of fatal tuberculous meningitis at a point shortly before, and all the way up to, death.

Persisting high sedimentation rates in the presence of persisting high gamma globulin levels occurred in several patients, all of whom did well clinically. And those in whom both the gamma globulin and the sedimentation rate fell together also had no complications.

Typical examples of cases showing the gamma-globulin-sedimentation-rate dissociation are shown graphically in Chart 7.

To illustrate this phenomenon further, Chart 8 plots the lowest levels of gamma globulin obtained against the sedimentation rate at that particular time in the 28 cases of benign primary tuberculosis as compared with the 19 cases of tuberculous meningitis. The low gamma globulin levels reached in the benign cases occur with correspondingly low sedimentation rates, while the low levels in the meningitic cases occur at the time of high sedimentation rates.

COMMENT AND SUMMARY

A study of the serum gamma globulin levels in various types of tuberculosis in children was made. It is recognized that the gamma globulin is nonspecific and varies considerably in many different diseases. Before attempting to evaluate it in any given patient with tuberculosis, other diseases affecting the gamma globulin level must be ruled out. It was not of value in diagnosis.

In all forms of tuberculosis the gamma globulin level was found to be elevated above normal levels fairly early in the disease. No difference was found between the streptomycin- and the nonstreptomycin-treated patients with pulmonary tuberculosis as to the height reached nor as to the time from onset of disease when the high levels were reached or normal levels regained. No differences were found with regard to race or sex. No relation was found to the hematocrit reading or total white blood cell count. High monocyte counts were often found with elevated gamma globulin levels. Increasing levels of gamma globulin were found regularly with increasing age.

In uncomplicated primary pulmonary tuberculosis, and in tuberculosis with effusion, peak elevations of gamma globulin were reached at about the sixth week, with return to normal values by about the 20th week. This paralleled the course of the sedimentation rate, but the latter rose a little earlier and returned to normal earlier. In reinfection tuberculosis the high levels of gamma globulin were maintained for longer periods, probably owing to the fact that these cases remained active longer. In tuberculous adenitis, the highest single level of gamma globulin obtained in the entire series was reached and the levels were maintained for the longest periods. This agrees with the theory of gamma globulin being the product of the reticuloendothelial system, as lymph nodes are made up largely of reticuloendothelial elements.

Cases of bone tuberculosis showed the lowest gamma globulin levels. Cases of miliary tuberculosis without meningitis showed very high levels of gamma globulin, and it may be that these good levels of gamma globulin represented good antibody

response, and help to explain how the patients avoided meningitis in spite of having miliary tuberculosis.

Cases of tuberculous meningitis (including those cases developing as complications of pulmonary tuberculosis) showed initial rises in gamma globulin just as the other forms of tuberculosis. However, in most of these cases there was a gamma-globulin-sedimentation-rate dissociation just before the onset of the meningitis and just before death, with the gamma globulin falling rapidly and the sedimentation rate rising.

CONCLUSIONS

The serum gamma globulin level follows a characteristic curve in cases of tuberculosis in children, rising early in the course of the disease and returning to normal later during convalescence. The high levels reached increase with age during early childhood. The serum gamma globulin, when followed serially and in conjunction with the sedimentation rate, is a valuable index of immediate prognosis. A falling gamma globulin occurring with a rising sedimentation rate is a bad prognostic sign, indicating decreased body resistance and/or increased disease activity, and is an indication for immediate diagnostic and therapeutic measures. A single gamma globulin determination is of no prognostic significance, high levels having been found early in the course of cases which later ended fatally

A COMMUNITY STUDY OF RHEUMATIC FEVER

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STUDENTS of rheumatic fever disagree in regard to adequate clinical and laboratory criteria for diagnosis during various stages of the disease. Because geographic location, climate, altitude, age, genetic factors, duration of the disease, and other variables enter into the complex picture of rheumatic fever, the correct diagnosis often eludes detection for some time. Studies of the clinical nature of this disease are needed. It is *sine qua non* that experimental observations be made from a clearly defined source. An accurate diagnosis is equally important to the clinician who is concerned with the evaluation of treatment programs designed to limit the crippling and lethal effects of progressive rheumatic carditis. The present study was undertaken, therefore, in order (*a*) to define the current clinical and laboratory picture of rheumatic fever in the Rochester area and (*b*) to describe the clinical material on which a large number of experimental observations have been based. It must be emphasized that we do not intend to propose a new classification of rheumatic fever. Our purpose is to describe the disease as it appears in the community and to define the source material from which experimental observations will be reported. The cases have been divided into arbitrary groups for purposes of description only.

MATERIAL

During the period July, 1949, to April, 1950, observations were recorded on children who had rheumatic fever, or a definite or suspicious history of the disease in any phase. All these children were admitted to the pediatric services of the five major general hospitals of Rochester, the Rochester Convalescent Hospital for Children, and the Rheumatic Fever Diagnostic Clinic of the Rochester Health Bureau. They were observed at frequent intervals during the entire study or for as long as possible. A few observations were recorded prior to July, 1949, and a few have been made since April, 1950. Control studies were made on nonrheumatic children admitted to the Strong Memorial and Rochester Municipal Hospitals and the Rheumatic Fever Diagnostic Clinic. Only children who did not have and were never known to have had clinical or laboratory evidence to support reasonable suspicion of rheumatic disease were accepted as control patients. Within the limitations of diagnostic fallibility, the cases were classified as indicated in Table 1.

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RESULTS

Detailed analysis of the large amount of clinical material will not be attempted at this time. A summary of pertinent clinical and laboratory observations follows.

Sex and Age Incidence.—Table 1 summarizes the sex and age incidence of cases in each group. The familiar preponderance of males over females is seen in the rheumatic groups. Among 75 patients with active or inactive rheumatic fever, 45 (60%) were male. Thirty-five (67.4%) of 52 patients with the active disease were male. The control series showed no sex predominance. The age incidence as recorded in the table is weighted by two factors: First, a number of adult patients from the Rheumatic Fever Diagnostic Clinic have been included. These patients fall into many groups but affect the smaller groups with rheumatic disease to a

TABLE 1.—*Classification of Patients and Distribution of Cases by Sex and Age (in Years)*

Group	Description	No. of Cases	Male	Female	Youngest	Oldest	Mean Age
I	Acute rheumatic fever, first attack	36	21	15	4	16	10.4
IIa	Protracted rheumatic fever, acute reactivation	9	7	2	7	16	12.4
IIb	Protracted rheumatic fever, subacute	7	3	4	7	24	12.2
III	Quiescent rheumatic fever	18	10	8	6	27	14.3
IVa	Chorea, no supporting evidence of rheumatic fever	2	2	0	6	17	11.5
IVb	Same as IVa, but chorea doubtful	6	3	3	7	13	10.7
Va	Suspected rheumatic fever, acute or protracted	35	19	16	3	18	9.3
Vb	Rheumatic fever, doubtful activity	5	4	1	13	20	15.6
Ve	Quiescent rheumatic fever, diagnosis of original rheumatic fever uncertain	29	16	13	7	24	11.9
VI	Congenital heart disease, no rheumatic fever	14	10	4	2	16	7.7
VII	Acute infectious diseases	70	35	35	1 wk.	56	6.8
VIII	Miscellaneous diseases	35	17	18	5 mo.	19	8.3
IX	Normal children	81	44	37	2 wk.	23	8.2
Total number of patients		347					
Total cases of rheumatic fever, active and quiescent (I, IIa, IIb, III, Vb)		75					
Total cases of rheumatic fever, active (I, IIa, IIb, Vb)		57					
Total cases of doubtful rheumatic fever, active and quiescent (Va, Ve)		64					
Total cases, control (VII, VIII, IX)		168					

greater degree. Second, a larger number of younger children have been included in the control groups. Therefore, comparisons of age incidence cannot be made.

Seasonal Variations.—Most acute rheumatic episodes occurred during the winter and spring months. Fewer acute attacks were seen during the summer and autumn, although evidence of continuing low-grade rheumatic activity was seen in many patients during these seasons.

Economic Level.—Rheumatic fever has long been recognized as a disease of the underprivileged, although it occurs at all social levels. Our cases were divided into three economic groups: those occurring in families with an annual income of less than $2,000, those from families with annual incomes of between $2,000 and $4,000, and those cases occurring in families whose yearly income exceeded $4,000. The results are summarized in Table 2. In this community rheumatic fever occurred largely in the middle income group. Relatively few cases occurred in either the lower or the higher income categories. However, 20% of patients in the unselected control series came from families in the upper income group.

Family History.—Table 3 shows the incidence of rheumatic fever by history in the families of patients in the rheumatic and control groups. The disease occurred much more frequently in the families of rheumatic children. Multiple cases of the disease were especially likely to occur in these families. We believe that failure to obtain a family history of rheumatic fever does not weigh against the diagnosis in

TABLE 2.—*Distribution of Cases According to Annual Family Income*

Group	No. Cases	< $2,000	$2,000-$4,000	> $4,000
I	21	3	17	1
IIa	5	1	4	0
IIb	4	0	3	1
III	8	0	7	1
IVa	2	0	2	0
IVb	3	0	3	0
Va	21	2	16	3
Vb	3	0	3	0
Vc	7	1	4	2
VI	8	0	6	2
VII	39	4	25	10
VIII	13	1	10	2
IX	38	6	26	6
Total cases of rheumatic fever *	41	4 (9.8%)	34 (82.9%)	3 (7.3%)
Total controls	98	11 (11.2%)	67 (68.4%)	20 (20.4%)

* Doubtful cases not included.

TABLE 3.—*Incidence of Rheumatic Disease in the Family History*

		Family History of Rheumatic Fever			
		Positive			
Group	No. Cases	Total	Multiple Cases	Equivocal	Negative
I	27	10	3	3	14
IIa	6	2	1	2	2
IIb	6	2	0	0	4
III	17	5	0	1	11
IVa	2	1	0	0	1
IVb	6	1	1	1	4
Va	33	8	3	8	17
Vb	5	0	0	1	4
Vc	25	4	2	3	18
VI	12	2	0	1	9
VII	60	7	0	7	46
VIII	27	2	0	1	24
IX	69	5	1	12	52
Total cases of rheumatic fever *	61	19 (31.2%)	4 (6.6%)	7 (11.5%)	35 (57.4%)
Total controls	168	16 (9.5%)	1 (0.6%)	21 (12.5%)	131 (78.0%)

* Doubtful cases not included.

any patient; however, a strongly positive family history of the disease may be considered important in certain otherwise doubtful cases.

Respiratory Infection.—Table 4 summarizes the frequency of respiratory infections in the various clinical groups. The reliability of histories of the frequency of respiratory infection is questionable. However, respiratory disease seems somewhat more prevalent among children with active rheumatic disease than among those with the quiescent disease or the control patients.

Bacteriologically proved hemolytic streptococcal infection accompanied or preceded the acute attack in six cases in Groups I and IIa. Four cases of concurrent or recent streptococcal infection occurred in the control groups, in two of which the

TABLE 4.—*Frequency of Respiratory Infection by History*

Group	No. Cases	FURI *	IURI †
I	30	12	18
IIa	6	1	5
IIb	5	2	3
III	16	4	12
IVa	1	1	0
IVb	6	5	1
Va	32	8	24
Vb	5	1	4
Vc	26	10	16
VI	12	5	7
VII	65	16	49
VIII	32	4	28
IX	72	26	46
Total cases of rheumatic fever ‡	62	20 (32.3%)	42 (67.7%)
Active cases of rheumatic fever ‡	41	15 (36.6%)	26 (63.4%)
Total controls	181	51 (28.2%)	130 (71.8%)

* FURI indicates "frequent" upper respiratory infections by history.
† IURI indicates "infrequent" upper respiratory infections by history.
‡ Doubtful cases not included.

TABLE 5.—*Tonsillectomy and Adenoidectomy*

Group	No. Cases	Total Tonsillectomy and Adenoidectomy	Tonsillectomy and Adenoidectomy Preceding 1st Attack
I	28	11	9
IIa	6	3	1
IIb	3	2	1
III	13	9	6
IVa	0	0	0
IVb	4	2	1
Va	27	17	10
Vb	5	1	0
Vc	26	15	12
VI	11	4	..
VII	66	15	..
VIII	32	6	..
IX	60	20	..
Total cases of rheumatic fever *	55	26 (47.3%)	18 (69.3%)
Active cases of rheumatic fever *	37	16 (43.3%)	11 (68.8%)
Total controls	169	45 (26.6%)	..

* Doubtful cases not included.

diagnosis was verified bacteriologically. The picture may not be representative, however, since many cases were not completely studied in this respect.

Tonsillectomy and Adenoidectomy.—Tonsillectomy was performed in a much higher proportion of rheumatic children than controls. In more than half tonsillectomy preceded the onset of the first rheumatic attack, as shown in Table 5. Removal of tonsils and adenoids had no obvious effect on the course of rheumatic disease.

Mortality.—One patient in the series died during an acute, fulminating rheumatic episode. Severe pancarditis was evident clinically and at autopsy. This was the patient's first clinical attack, at the age of 4 years (Group I), although postmortem examination revealed old mitral vegetations, indicating earlier undiagnosed rheumatic disease. Mortality analysis is summarized in Table 6. None of the control patients died.

TABLE 6.—*Mortality*

Group	No. Cases	No. Deaths	Mortality, %
I (acute rheumatic fever, first attack)	35	1	2.8
I, IIa, IIb (total, active rheumatic fever)	52	1	1.9
I, IIa, IIb, III, Vb (total rheumatic fever, active and quiescent)	75	1	1.3

TABLE 7.—*Incidence of Outstanding Rheumatic Symptoms, Group I (Acute Rheumatic Fever, First Attack)**

Symptom	NCE	NCES	% Incidence	±	+	++	Absent	% Absent
Fever	36	31	86.2	1	6	25	4	11.1
Joint pain	36	29	80.6	1	2	27	6	16.7
Arthritis	36	26	72.2	0	0	26	10	27.8
Easy fatigue	25	17	68.0	2	2	15	6	24.0
Pallor	24	14	58.3	2	5	9	8	33.3
Behavior changes	17	9	52.9	5	1	8	3	17.6
Abdominal pain	36	13	36.1	0	4	9	23	63.9
Chorea	36	7	19.4	1	0	7	28	77.8

* NCE indicates number of cases evaluated for each symptom; NCES, number of cases exhibiting symptom among those evaluated; ±, symptom equivocal, number of cases; +, symptom present, number of cases (not including number in which symptom was outstanding [++]); ++, symptom outstanding, number of cases, and %, percentage incidence in total number of cases evaluated.

TABLE 8.—*Incidence of Outstanding Rheumatic Symptoms, Group Va (Suspected Rheumatic Fever)**

Symptom	NCE	NCES	% Incidence	±	+	++	Absent	% Absent
Easy fatigue	31	20	64.6	3	18	2	8	25.8
Joint pain	35	20	57.2	2	17	3	13	37.2
Arthritis	35	5	14.3	4	4	1	26	74.3
Abdominal pain	35	13	37.2	0	13	0	22	62.8
Fever	35	12	34.3	6	12	0	17	48.6

* For explanation of headings, see footnote to Table 7.

CLINICAL MANIFESTATIONS

The frequency of symptoms and signs as recorded in Tables 7 and 8 and in the accompanying text is indicated as percentage incidence in the number of cases in each group for which information regarding the item is available.

Acute Rheumatic Fever, First Attack: Group I (Thirty-Six Cases).—Table 7 summarizes the incidence and severity of the most important symptoms seen in patients of Group I. All patients had fever except four with active rheumatic chorea. The character, duration, or degree of fever was of no diagnostic importance. Joint pain occurred in 80.6% of patients. Objective evidence of arthritis was found in all but three of these persons. Joint involvement was multiple in most patients, although migrating polyarthritis was not common. Joint manifestations were generally less

typical in younger children. The single patient in this group who died, a 4-year-old girl, had no symptoms of joint involvement at any time. Chorea was an outstanding symptom in four of the patients in whom joint manifestations were absent.

A marked degree of easy fatigability and pronounced pallor were frequent and notable symptoms. Abdominal pain and emotional instability or changes in behavior or habit patterns were important symptoms in this group, particularly in younger patients. Chorea occurred as a clearly rheumatic symptom in 20% of patients. Other clinical evidences of rheumatic disease appeared sporadically and in the following order of decreasing frequency: spontaneous epistaxes, muscle pains, weight loss, pericarditis, rheumatic pneumonia, pleuritis, and erythema marginatum. No case of nephritis was encountered.

The pulse rate in the present group ranged from 70 to 150 per minute, with an average of 111. However, inconstant conditions of observation made an evaluation of heart rate impossible.

Clinical evidence of well-established endocarditis was found in five cases (13.9%), was equivocal in 11 (30.6%), and was absent in the remaining 20 (55.6%). This suggests that the first clinical attack of acute rheumatic fever does not represent the first experience with the disease in many of these children. Subacute bacterial endocarditis and subcutaneous nodules were not found in this group.

The difficulty and unreliability of attempting to assess the presence or degree of acute carditis in patients with infectious disease have been cited in an earlier publication.[1] Present observations on rheumatic fever confirm this impression. The criteria considered in evaluating acute carditis were the following: (*a*) lability of the pulse rate, with marked and sustained changes in heart rate on minimal stimulation, (*b*) evanescent and changing equality of heart sounds and murmurs from beat to beat and day to day, and (*c*) the presence of tick-tack rhythm or embryocardia, with audible lengthening of systole and a shortened diastolic interval. Evidence of progressive endocarditis, progressive enlargement of the heart or its specific chambers, the occurrence of cardiac decompensation, and failure of adequate therapy were also considered in attempting to establish the presence and severity of acute carditis. Attempts to evaluate the degree of carditis were generally unreliable, except in the severer cases in which the diagnosis was obvious. In milder cases carditis could often be strongly suspected, but differences of opinion among observers emphasized the inherent subjective limitations of such observations. The criteria are helpful and important and will, with practice, increase diagnostic acumen, but no single criterion or combination of criteria established a correct diagnosis in every case.

Laboratory studies revealed fluctuation of the white blood cell count from 4,900 to 17,500 per cubic millimeter. The lower counts occurred in patients with chorea. The average white blood cell count was 11,300. There was usually a predominance of neutrophils. Hemoglobin values ranged from 10.5 to 14.5 gm. per 100 cc. (Sahli), with an average value of 12.8 gm. per 100 cc. The Wintrobe erythrocyte sedimentation rate ranged from 10 to 55 mm. per hour, with a mean of 30.9 mm. During the acute phase of the attack, sedimentation rates always exceeded 20 mm. per hour except in four cases of rheumatic chorea. Vital capacity

1. Joos, H. A., and Yu, P. N. G.: Electrocardiographic Observations in Poliomyelitis, Am. J. Dis. Child. **80**:22 (July) 1950.

measurements in eight patients according to Wilson's method [2] revealed values of less than—20% in only two instances. The antistreptolysin O titer was greater than 250 units in each of the 27 cases in which it was measured. The highest titer was 1,500 units, and the average for the group was 687 units. Antihyaluronidase titers ranged from 160 to 1,280 units in nine cases. Antistreptolysin O and antihyaluronidase titers could not be related to the severity of the disease.

Roentgenography was performed for 24 patients. Results of fluoroscopy were not recorded in every case. Generalized cardiac enlargement in five cases, and specific enlargement of the pulmonary conus, left auricle, or left ventricle in six additional cases were reported. Sixteen patients had a normal appearance on roentgenologic examinations.

Varying numbers of electrocardiograms were made on all patients. Sinus tachycardia with heart rate greater than 140 a minute was seen in tracings from two patients. One patient had premature nodal contractions; another had premature supraventricular and premature ventricular contraction. First-degree heart block was noted in 22 patients (61.1%) at some time during the acute attack. Electrocardiographic evidence of left and right ventricular hypertrophy was seen in one patient each. Marked left axis deviation occurred in one patient. Four patients (11.1%) showed ST and T wave changes suggesting myocardial disease. The presence of pericarditis was suggested from the tracings for two patients. The transient nature of the heart block or rhythm abnormalities could not be established in every case. The Q-Tc interval was measured but was not considered in classifying the present cases. Data regarding the diagnostic value of the Q-Tc interval will be presented in a subsequent publication. No electrocardiographic changes could be considered of uniform and specific diagnostic value in determination of the presence or severity of carditis.

Protracted Rheumatic Fever, Acute Reactivation: Group IIa (Nine Cases).—The symptoms and signs of active rheumatic fever in this group were similar to those in Group I. Joint pains, polyarthritis, and fever were the most frequent and outstanding symptoms. Pallor, marked fatigability, and epistaxes were noted in a high proportion of cases. There were two cases of rheumatic chorea in this group. Rheumatic pneumonia occurred once, and pleuritis was suspected in one other case. Behavior changes were not pronounced in this group. Clear clinical evidence of endocarditis was noted in five cases, was equivocal in one, and could not be demonstrated in three. Subcutaneous nodules were not found, and subacute bacterial endocarditis did not occur during the period of observation. The first rheumatic attack had taken place between the ages of 3 and 14 years, with an average age of 9.9 years. There had been one to four previous attacks, an average of 2.5 attacks a patient. Attacks had lasted 2 to 11 months, with an average duration of 5.7 months. Carditis could be diagnosed more accurately than in Group I, but again the severest cases were most apt to be correctly evaluated. It should be noted that a correct evaluation could be so judged only by the subsequent course of the disease. The short period of study, therefore, limits the reliability of these observations. Laboratory findings were similar to those for Group I. However, there was a greater preponderance of neutrophils on the blood smear (80% average); the antistreptolysin O titer was consistently elevated to higher levels (range, 250 to 2,500

2. Wilson, M. G.: Rheumatic Fever, New York, The Commonwealth Fund, 1941.

units; average, 880 units), and the vital capacity in two patients was measured at —25% and —37%. Roentgen examination revealed generalized or specific cardiac chamber enlargement in all five patients on whom such examination was made. There were no abnormalities of rhythm in the electrocardiograms of these patients. Four patients showed delayed auriculoventricular conduction time, in one of whom interference dissociation was noted. Prolongation of the P-R interval was known to be transient in two patients and was believed to be permanent in two. The remaining five patients showed no auriculoventricular conduction abnormality. Right axis deviation was found in one patient.

Protracted Rheumatic Fever, Subacute: Group IIb (Seven Cases).—As expected, the usual symptoms and signs of active rheumatic fever were not prominent in this group. History and results of examination often suggested doubtful or nonspecific illness. Marked fatigability was constant, and pallor was often notable. Joint pains were pronounced in one patient, vague in two others, and absent in three. Objective arthritis did not occur in this group. Muscle pain could not always be differentiated from joint discomfort. Abdominal pain, weight loss, pneumonitis, and spontaneous epistaxes occurred but were neither outstanding nor consistent. Rheumatic fever first attacked these patients at the age of 5 to 11 years (average age of onset, 8 years). They had experienced one to five acute attacks (average, 1.6 attacks) lasting one to nine months (average, 4.5 months). Endocarditis was clearly established in three patients, was doubtful in one patient, and could not be detected in the remaining three patients. Subcutaneous nodules were not found, and subacute bacterial endocarditis did not occur. One patient had rheumatic chorea. The estimated duration of rheumatic fever ranged from 5 to 168 months (average, 45 months). Active carditis was detected clinically in three of five patients on whom sufficient observations could be made. Such considerations as progressive endocarditis, progressive cardiac enlargement, and the occurrence of cardiac decompensation are of greater diagnostic value in cases of protracted rheumatic disease of long standing. Laboratory findings were not helpful in this group. The white blood cell count, the differential count, and the hemoglobin values were normal. The Wintrobe sedimentation rate ranged from 6 to 24 mm. (average, 12 mm.) per hour. The vital capacity was variable. Antistreptolysin O titers were low in two patients. One patient had generalized cardiac enlargement on roentgen examination; one showed equivocal enlargement of the pulmonary conus, and the hearts of two were normal on examinations. Electrocardiograms showed one instance each of sinus bradycardia and premature supraventricular contractions. ST-T wave changes suggested possible myocardial damage in one patient. The P-R interval was normal for age and heart rate on all tracings.

This group of patients, though small, was difficult to evaluate for rheumatic activity. The decision is critical, however, since these are patients for whom the risk may be grave if ambulation is begun before complete cessation of rheumatic activity. The number of these cases in the community is certainly larger than this series indicates. However, we have been rigid in our classification, and the many doubtful cases are considered elsewhere (cf. Groups Va, Vb, and Vc).

Quiescent Rheumatic Fever: Group III (Eighteen Cases).—Patients in this group had a clear history of earlier acute rheumatic fever but had no evidence of rheumatic activity during the period of observation. Four patients (23.5%) complained of undue fatigue. Spontaneous epistaxes occurred in three patients (17.6%),

repeatedly in two of these. One patient had fever which was not rheumatic in origin. Vague muscle and joint discomfort occurred in one patient without supporting evidence of rheumatic activity. Rheumatic fever first attacked these patients at ages ranging from 4 to 26 years (average, 9.6 years). They had suffered an average of 1.2 acute attacks each. Acute attacks had lasted an average of 9.9 months. Endocarditis was definite in six patients (33.3%), equivocal in three (16.6%), and not detectable in nine (50.0%). Subcutaneous nodules were not found, and subacute bacterial endocarditis was not observed. No patient had clinical findings suggesting active carditis. Laboratory studies gave essentially normal results. Two patients had an antistreptolysin O titer of 250 units. Titers of six others were lower. Roentgenologic evidence of general cardiac or specific chamber enlargement was noted in five patients (41.7%) and was equivocal in three (25.0%). Four patients had hearts of normal size and configuration. The electrocardiogram revealed sinus bradycardia and a permanently prolonged P-R interval in one case each and questionable auriculoventricular conduction delay in two cases.

Chorea: No Supporting Evidence of Rheumatic Fever: Group IVa (Two Cases).—The diseases of two patients with moderately severe chorea but no clinical or laboratory evidence of rheumatic fever were classified clinically as examples of "pure chorea." No evidence of carditis or of visceral rheumatism was found, and no roentgenologic or electrocardiographic abnormalities were demonstrated.

Doubtful Chorea: No Supporting Evidence of Rheumatic Fever: Group IVb (Six Cases).—Chorea could be neither established nor excluded in these cases, and a diagnosis of past or present rheumatic fever could not be made with certainty. Changes in behavior patterns were notable; marked fatigue and muscular pain were less frequent. Joint pain was equivocal in three patients, and abdominal pain was prominent in one. None had clinical evidence of carditis or laboratory findings suggesting rheumatic activity. Low vital capacity readings for four patients may reflect difficulties in muscular coordination. Normal appearance on roentgen examination was reported for five patients. One patient showed a prominent pulmonary conus and doubtful enlargement of the outflow portion of the right ventricle. One patient had an apparently permanent delay in auriculoventricular conduction on the electrocardiogram.

Suspected Rheumatic Fever, Acute or Protracted: Group Va (Thirty-Five Cases).—A definite diagnosis of rheumatic fever could be neither made nor excluded in these cases, using the usual clinical and laboratory criteria. Table 8 summarizes the incidence of rheumatic symptoms. Marked fatigability and joint discomfort were the most frequent and prominent symptoms. Five patients had definite and four had equivocal objective evidence of arthritis. Abdominal pain, fever, muscle pain, behavior changes, pallor, and spontaneous epistaxes occurred less frequently in order of decreasing incidence. The average duration of symptoms at the time of first observation was 7.7 weeks. The average age at the onset of symptoms suggesting rheumatic fever was 8.5 years. Clinical evidence for the presence of established endocarditis was equivocal in two cases. The presence of mild chorea could be neither established nor excluded in two other cases. Clinical evidence of active myocarditis was scattered and equivocal and in every case was insufficient to support a diagnosis of active rheumatic disease. A white blood cell count in excess

12,000 occurred in four cases, and the average white blood cell count was 8,600. Hemoglobin values were generally normal. The Wintrobe sedimentation rate varied from 4 to 34 mm. (average, 15.8 mm.) per hour. Vital capacity measurements in 21 cases ranged from +5% to less than —40% and did not appear to have specific diagnostic value. Antistreptolysin O titers in 29 cases varied from 0 to 1,250 units (average, 257 units). Antihyaluronidase titers ranged from 0 to 160 units (average, 23 units) in 21 cases. Roentgenologic examination suggested doubtful enlargement of the cardiac silhouette or its chambers in 8 cases (32%), and the cardiac configuration was recorded as normal in 17 cases (68.0%). Electrocardiograms showed prolonged auriculoventricular conduction time in two patients, in one of whom the abnormality was apparently permanent; in the other the sign was known to be transient. The P-R interval was of borderline duration for age and heart rate in five cases (15.1%). Frequent sinoauricular blocks were seen in two cases, and left axis deviation, premature supraventricular contractions, wandering pacemaker, and slurred QRS complex were seen in one case each. One patient had hypertension (blood pressure, 120/100). In no case could a diagnosis of rheumatic fever be made beyond reasonable doubt. However, no satisfactory alternative diagnoses were made for these patients' conditions during the period of observation.

Rheumatic Fever, Doubtful Activity: Group Vb (Five Cases).—Patients of this group had had rheumatic fever, and continuing low-grade rheumatic activity could not be excluded. Marked fatigability and episodes of abdominal pain occurred in one patient. Another had a recurrence of chorea without other signs of rheumatic activity. Definite symptoms or signs of rheumatic activity were lacking, and these patients had few specific complaints. Endocarditis was present in four of the patients and was thought to be progressing in all. Progressive cardiac enlargement and failure to respond to adequate therapy were suspected in one patient each. Other clinical evidence of active carditis was not definite in any patient. Rheumatic fever began at an average age of 10.6 years, and each patient had had an average of 1.4 attacks, lasting an average of 54 weeks each. Wintrobe sedimentation rates ranged from 4 to 37 mm. (average, 18.6 mm.) per hour. The antistreptolysin O and antihyaluronidase titers were variable as in other rheumatic groups and were not helpful in evaluating activity. Cardiac enlargement was shown on roentgenograms in four cases (80%). The cardiac configuration of one patient was reported as normal. Sinus escape, occurring in one patient, was the only electrocardiographic abnormality.

Quiescent Rheumatic Fever, Uncertain Original Diagnosis: Group Vc (Twenty-Nine Cases).—An earlier diagnosis of rheumatic fever had been made in patients of this group in uncertain circumstances. No objective evidence of earlier rheumatic disease or of current rheumatic activity was obtained. Twelve patients (42.8%) complained of marked fatigability; six (20.7%) had some joint discomfort; six (22.2%) showed changed behavior patterns; three had muscular aches and pains; three had some abdominal pain. There were two instances of fever and one of spontaneous epistaxis. There was no clinical evidence of cardiac damage or current carditis. Laboratory findings did not support a diagnosis of rheumatic fever. Roentgen study revealed no clear case of generalized cardiac or specific chamber enlargement, although equivocal interpretations were made in six patients (27.3%). Electrocardiograms demonstrated sinus bradycardia and right axis deviation in one patient each.

Congenital Heart Disease: Group VI (Fourteen Cases).—No patient in this group had a superimposed rheumatic infection. Group VI is included as a control series for purposes of comparison only. Marked fatigability occurred in five patients. Joint discomfort, muscular aches and pains, fever, and spontaneous epistaxes were uncommon and occurred separately. No clinical or laboratory findings suggested old or current carditis. Roentgenographic and electrocardiographic abnormalities were frequent and often bizarre. Included in the latter is auriculoventricular conduction delay, which occurred in two patients and was equivocal in three others. In two instances the prolonged P-R interval was transient.

Acute Infectious Diseases: Group VII (Seventy Cases).—The data on this and the two succeeding groups constitute a series of control observations that are intended to provide a baseline from which a number of experimental comparisons can be made. These studies will appear in subsequent publications.

Group VII includes patients with a variety of acute infectious diseases taken at random from the hospital population. No patient had rheumatic fever, although the diagnosis had to be excluded in several cases. The nonspecific character of many so-called rheumatic symptoms is illustrated by their frequency in this group. Fever, of course, was the commonest symptom, occurring to a significant degree in 65 patients (92.9%). Joint discomfort was noted in 14 patients (20.0%) and was pronounced in 12 (17.1%), of whom 6 had objective evidence of arthritis. Muscle pain occurred in 28 patients (41.8%). There were 11 patients (16.2%) with marked nonsurgical abdominal pain. Pronounced fatigability, behavior changes, pallor, and spontaneous epistaxes were less common. Acute myocarditis was suspected clinically in three patients, two of whom had acute poliomyelitis and the other osteomyelitis due to Staphylococcus pyogenes var. aureus. Laboratory findings reflected the infectious process in the individual case. It is of interest that four of five vital capacity measurements resulted in values of —20% or less. Roentgen examination of 17 patients revealed questionable cardiac chamber enlargement in 2 instances. Neither patient had clinical or electrocardiographic evidence of carditis. Sinus tachycardia in excess of 140 per minute was demonstrated on the electrocardiograms for six patients of 68. Auriculoventricular conduction delay occurred in four patients, was transient in two of these, and was believed permanent in one. Transient prolongation of the P-R interval was associated with clinical evidence of acute carditis in one patient with acute poliomyelitis. Premature ventricular contractions were encountered in one patient. Right axis deviation occurred in five patients. Apparently abnormal ST segments and T waves were seen on tracings for three patients, occurring with marked sinus tachycardia and right axis shift in one patient and with a prolonged P-R interval and low voltage in another. These patients had acute poliomyelitis and urinary infection, respectively. Myocardial ischemia was questioned in the electrocardiogram of the latter patient, a 56-year-old woman.

Miscellaneous Diseases: Group VIII (Thirty-Five Cases).—Endocrine, neurologic, allergic, hematologic, and nutritional diseases, congenital abnormalities, and metabolic disorders are included in this group. Possible rheumatic symptoms were less common. Behavior changes and fever were each present in eight patients (15.2 and 14.3%). Objective arthritis was noted in two patients, one of whom had hemophilia and the other disseminated lupus erythematosis. Marked fatigue,

excessive pallor, muscle pains, and spontaneous epistaxes were not common. Carditis was clinically suspected only in the patient with lupus. Roentgen examination was made on five patients, in two of whom slight cardiac chamber enlargement was questioned. Neither patient exhibited supporting evidence of cardiovascular disease. Transient prolongation of the P-R interval and ST and T wave abnormalities were observed in the electrocardiogram of the lupus patient, a 13-year-old child who showed persistent and pronounced hypopotassemia. ST and T wave abnormalities were also seen in the tracing of a 13-year-old child with a conversion hysteria and in that of an 8-year-old child with suspected adrenogenital syndrome whose electrocardiogram also showed low voltage. These changes are unexplained. Right axis deviation occurred only in the latter patient.

Normal Children: Group IX (Eighty-One Cases).—Patients in this group had no definite clinical evidence of disease during the period of observation. Possible rheumatic symptoms were uncommon. Sixteen of these patients (20.3%) complained of easy fatigue. Joint discomfort occurred in six patients (7.6%). Muscle pains, pallor, behavior changes, abdominal pain, and spontaneous epistaxes were uncommon. No patient had clinical signs of old or recent carditis. Laboratory findings were generally normal. There were scattered elevations of the antistreptolysin O titers above 250 units. Vital capacity was measured in 56 patients and was —20% or less in 27 of them (48.3%). Roentgenologic examination was performed on 45 patients, and equivocal cardiac enlargement was noted in 10 of these. Electrocardiograms were made on 79 patients, of whom 4 had sinus bradycardia and 1 a marked sinus tachycardia. Occasional premature supraventricular contractions were seen in one case. Delayed auriculoventricular conduction was observed in two cases and was transient in one of these. The P-R interval was equivocally prolonged for age and rate in two additional patients. Right axis shift was noted in four patients. A question of right ventricular hypertrophy was raised from the electrocardiograms of two patients.

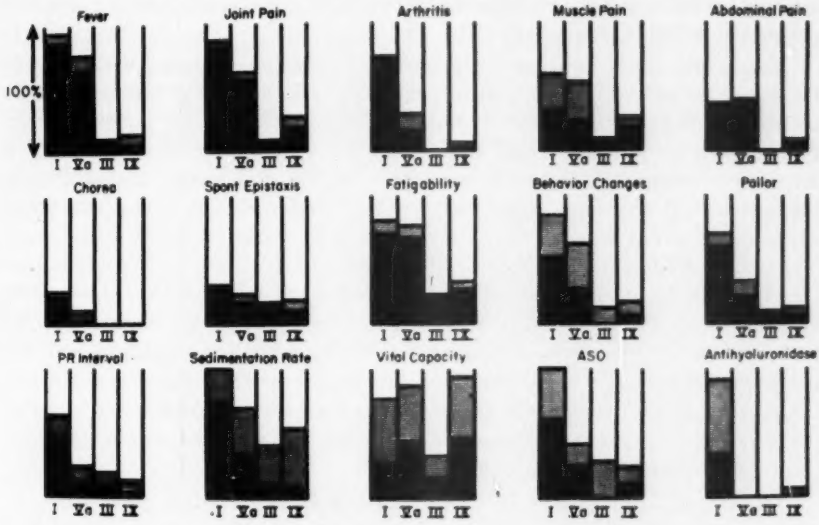
COMMENT

The Chart compares the percentage incidence of key rheumatic symptoms, signs, and laboratory findings in Groups I (acute rheumatic fever, first attack), Va (suspected rheumatic fever), and IX (normal children). The critical group of subacute cases is not included because of its small size. Generalizations can be made from such comparisons only with caution. Factors such as season, age, and duration of disease, may influence the course of rheumatic fever and its manifestations. Such influences are not represented, and group comparisons may, therefore, be oversimplified. However, the diagnosis of acute rheumatic fever may be facilitated by attention to fever, joint pain, arthritis, abdominal pain, chorea, fatigability, behavior changes, pallor, the P-R interval of the electrocardiogram, the erythrocyte sedimentation rate, the antistreptolysin O titer, and the antihyaluronidase titer. Measurement of the vital capacity was not helpful in our experience. The multiplicity of these items emphasizes the diagnostic uncertainty. The problem is greatly magnified in the more subtle cases of low-grade rheumatic activity.

Taran [3] has recently reviewed the clinical manifestations and many of the laboratory changes occurring during the prolonged course of rheumatic fever. This study

3. Taran, L. M.: Clinical and Laboratory Diagnostic Criteria of Rheumatic Fever in Children, Am. J. Med. **2**:368, 1947.

of a large group was made under well-controlled conditions in a sanatorium. The limitations and pitfalls of any rigid set of diagnostic criteria are pointed out; attention is directed to the less obvious but widespread visceral manifestatons of the disease; the difficulty and importance of accurate detection of active carditis at all stages are reemphasized. The disease is viewed broadly, and special attention is directed to observation of the patient as a source of information. We are reminded that laboratory procedures are often helpful but seldom are diagnostic. Other recent studies [4] have emphasized the lack of uniformity in the study of this disease, the limitations of statistical evaluations because of diagnostic fallibility, and the need for a perspective which searches out obscure evidences of low-grade, damaging rheumatic activity. It is obviously most difficult to study a disease which is such a



Comparison of the incidence of diagnostic findings according to groups of patients with rheumatic fever and normal controls. White areas indicate symptom absent; P-R interval normal; sedimentation rate of less than 10 mm. per hour; vital capacity of positive percentage; antistreptolysin O titer (*ASO*) of less than 250 units, and antihyaluronidase titer of less than 1:160.

Shaded portions indicate symptom equivocal; P-R interval of equivocal length; sedimentation rate of 10 to 20 mm. per hour; vital capacity of 0 to —19%; antistreptolysin O titer of 250 to 499 units, and antihyaluronidase titer of 1:161 to 1:639.

Solid portions indicate symptom present; P-R interval prolonged; sedimentation rate of more than 20 mm. per hour; vital capacity of —20% or less; antistreptolysin O titer of 500 units or more, and antihyaluronidase titer of 1:640 or more.

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4. Guy, P.: Some Difficulties of the Rheumatic Fever Problem, Northwest Med. **48**:845, 1949. McMillan, R. L., and Jones, C. C.: Rheumatic Heart Disease in Northwest North Carolina, North Carolina M. J. **11**:105, 1950. Rheumatic Fever in Children, Its Recognition and Management, Metropolitan Life Insurance Company, New York. Wilson, M. G., and Lubschez, R.: Longevity in Rheumatic Fever, Based on Experience in 1,042 Children Observed Over Period of 30 Years, J. A. M. A. **138**:794 (Nov. 13) 1948. Thornton, C. E.: Rheumatic Carditis in Children, M. Press **221**:117, 1949. Koenig, L. J.; Weaver, T. S.; Childers, A., and Woods, H. S.: Rheumatic Fever in Tennessee, South. M. J. **43**:199, 1950. Barnes, G.: An Investigation of Rheumatic Fever in Fiji, Tr. Roy. Soc. Trop. Med. & Hyg. **43**:413, 1950.

formidable diagnostic problem during much of its course. The need for continued effort to define rheumatic fever, clinically and in the laboratory, is clear.

The material presented offers primarily a picture of rheumatic fever as seen in a single community during a relatively short period of observation. It lacks the completeness which might be gained from prolonged observation under standard conditions. Therefore, no conclusion can be made regarding the evolution of the rheumatic process in various cases or in any group. Similarly, no inference regarding the prognosis of rheumatic fever can be made from the present study. In addition, the effects of treatment have not been considered. In general, no consistent treatment plan was employed. However, the patients were treated, and it is possible that the picture of the disease has been modified. No rheumatic patient received either cortisone or corticotropin (pituitary adrenocorticotropic hormone) during the period of observation.

Kaiser [5] has noted a decline in the incidence and severity of rheumatic fever in the Rochester area during the past 10 years. The relatively small number of cases and the insidious nature of the rheumatic disease in much of the material in the present study are in keeping with that observation. There is no certain explanation for such a change. It has been suggested that the widespread use of chemotherapeutic and antibiotic drugs early in the course of infections—particularly streptococcal infections—may have forestalled the rheumatic process in many cases. The prophylactic administration of sulfonamides and penicillin to susceptible persons may also be important in reducing the total number and perhaps the severity of acute rheumatic attacks. The rising standard of living in the community may be important for less apparent reasons. The disease itself may be changing. No one can guess the number of cases which continue to smolder below the horizon of clinical detection. A subsequent decline in late cardiac complications and sequelae will be required if our impression of the declining incidence and severity of rheumatic fever at present is to be confirmed.

The large group of cases in which a diagnosis of rheumatic fever could be neither confirmed nor excluded illustrates the diagnostic difficulties encountered in the present study. Opportunity for prolonged observation would doubtless shrink the group considerably. However, grave consequences may befall the rheumatic patient treated with too little restriction during the period of diagnostic doubt. On the other hand, considerable harm may be done to nonrheumatic patients treated and labeled as having a cardiac condition during the time that a diagnosis of rheumatic fever cannot be excluded. The dilemma challenges both the clinician and the researcher.

CONCLUSIONS

Rheumatic fever remains largely a clinical diagnosis. Laboratory aids are most useful in the light of a broad clinical experience with the disease. The careful observer will find that the patient is his most productive source of diagnostic information. The need for new knowledge of the nature of the disease, for more perceptive diagnostic tools, and for more effective treatment programs emphasizes the importance of understanding the clinical disease and its disguises as they affect whole patients, not merely hearts.

5. Kaiser, A.: Personal communication to the authors.

SUMMARY

During a large part of the prolonged course of rheumatic fever, the diagnosis may remain obscure and low-grade rheumatic activity may be undetected.

Uniform criteria for the diagnosis of rheumatic fever during all stages of the disease have not been established.

Rheumatic fever is classified and defined descriptively as it appeared in the Rochester area during 1949-1950. The clinical and laboratory features of rheumatic fever in its various phases are reviewed, and comparisons are made with similar observations in several control groups.

The importance of present diagnostic limitations is emphasized, and the need for understanding rheumatic fever as a disease affecting patients as a whole is cited.

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Dr. Nevin S. Scrimshaw and Dr. Roy Greer provided stimulus for this study. Dr. Paul N. G. Yu, Dr. Ralph Jacox, Miss Margaret Moen, Mrs. Noel Gray Lawson, Miss Caroline Gouverneur, and many others aided in this study. The active cooperation of the members of the staffs of the Genesee Hospital, the Rochester General Hospital, St. Mary's Hospital, and the Highland Hospital was indispensable and is acknowledged.

Case Reports

SCLEREMA NEONATORUM SUCCESSFULLY TREATED WITH CORTICOTROPIN (ACTH)

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SCLEREMA neonatorum is a diffuse hardening of the subcutaneous tissues occurring in undernourished, debilitated full-term and premature infants.[1] In an excellent review of the literature Hughes and Hammond[2] have summarized the significant findings of this condition as follows:

(1) Average age of onset was 4 days with extremes from birth to 70 days; (2) 25 per cent of the mothers were ill at the time of delivery; (3) all but two deliveries were spontaneous; (4) average birth weight was 2,800 Gm. with variations from 2,150 to 4,100 Gm.; (5) the majority of infants exhibited abnormal behavior at birth, weakness and cyanosis being the most common symptoms; (6) almost all children had difficulty with body temperature control and evidences of other complications besides sclerema; (7) 75 per cent died, with the average age of death 12 days; (8) eleven infants were autopsied, thickening of connective tissue bands being the most common finding.

Sclerema is a rare disease for which there has been no adequate treatment. Recently, however, Kendig and Toone[3] have reported recovery in a single instance following the use of cortisone.

The following case is that of an infant with sclerema neonatorum whose recovery was sufficiently rapid subsequent to therapy with corticotropin (ACTH) that a cause and effect relationship could be considered.

REPORT OF CASE

L., a Negro boy, was born in a taxicab en route to the hospital at 9:00 p.m. on June 9, 1951. The mother, the resident of another city, had gone into labor spontaneously while visiting relatives in Philadelphia. The prenatal course had been uneventful until the onset of labor in the afternoon of the day of delivery. The gestation period was approximately 30 to 32 weeks. The mother had given birth to a 4-lb. (1,800-gm.) premature infant in March, 1950.

The cord was severed and tied, and the eyes were treated with 1% silver nitrate solution in the receiving ward. Upon admission to the premature nursery the infant exhibited infrasternal retractions. The Moro reflex was present; the cry was fairly strong, but the breath sounds were poorly heard over the entire chest. Respirations were 40 a minute. The weight was 1,406 gm. (3 lb. 2 oz.), the length 45 cm. (17½ in), and the chest circumference 27 cm. (10½ in.). The infant was placed in an incubator (Isolette Infant Incubator) and oxygen supplied at the rate of 4 liters a minute. Because the delivery occurred under unsterile conditions, penicillin, 100,000 units, and dihydrostreptomycin, 20 mg., were administered intramuscularly every 12 hours. Five milligrams of vitamin K was also administered daily for a five-day period.

From the Department of Pediatrics, Temple University School of Medicine.

1. Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 5, Philadelphia, W. B. Saunders Company, 1950, p. 1539.

2. Hughes, W. E., and Hammond, M. L.: Sclerema Neonatorum, J. Pediat. **32**:676, 1948.

3. Kendig, E. L., and Toone, Jr., E. C.: Cortisone in the Treatment of Sclerema Neonatorum, A. M. A. Am. J. Dis. Child. **81**:771 (June) 1951.

During the first 24 hours of life the infant's condition was poor. Though there was no cyanosis, the respirations were labored and grunting, ranging from 60 to 80 a minute, and marked infrasternal retractions were present. The breath sounds were heard fairly well at times, but on other occasions very little air could be heard entering the lung fields. At 36 hours of age an absence of the Moro reflex and a firm hardening of the skin over the face, back, arms, and legs were noted. It was impossible to wrinkle the skin or to separate it from the subcutaneous tissues. A slight degree of pitting edema was present over the lower legs. At 5:00 p.m. on June 11, when the infant was 44 hours of age, 5 mg. of corticotropin was administered parenterally, and the dose was repeated at intervals of six hours for a total of eight injections.

By the next morning, when three doses of corticotropin had been administered, the infant's condition was dramatically improved; the respirations were no longer labored, and the rate had decreased to 40 a minute. Breath sounds were well heard throughout both lung fields, and the retractions of the chest wall had disappeared. The Moro reflex was present, and the degree of induration of the skin over the face, back, and extremities was greatly decreased. At this time, the infant being 60 hours of age, dextrose water feedings by gavage, 8 cc. every three hours, were started. Chloramphenicol (chloromycetin®), 25 mg. every six hours, was administered with the dextrose water feedings, and the parenteral administration of penicillin and streptomycin was discontinued. The induration of the skin decreased gradually and disappeared completely by June 14, when the infant was 108 hours of age and 64 hours had elapsed since the first dose of corticotropin. Chloramphenicol administration was discontinued on the sixth day of life.

The infant's temperature was maintained between 98 and 99 F. by means of a controlled environmental temperature of 90 to 92 F. within the incubator. Milk feedings of a high protein, low fat content were started on the fourth day of life. The infant was given a multivitamin preparation and additional ascorbic acid by the end of the first week. After the fifth day of life the neonatal course was uneventful; the feedings were taken well, and the weight gain was excellent. The infant was discharged from the hospital on the 27th day of life weighing 2,306 gm. (5 lb. 2 oz.) and appeared to be normal in all respects. Serologic tests for syphilis showed negative results, and a blood count on June 25 revealed 13.8 gm. of hemoglobin and 3,880,000 red cells.

SUMMARY

A case of sclerema neonatorum in a premature infant with dramatic recovery following corticotropin therapy is reported. A total dose of 40 mg. was administered intramuscularly over a period of 48 hours. The infant also exhibited respiratory distress, and these symptoms also disappeared promptly. The cure effected by corticotropin in this infant and the report of a patient successfully treated with cortisone [3] indicate that this form of therapy warrants further clinical trial.

Progress in Pediatrics

FACTORS TO BE CONSIDERED IN PLANNING A PREMATURE CENTER

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SINCE premature birth is the major cause of infant and neonatal mortality, many communities have set up or are in the process of planning programs designed to prevent premature birth and to provide better care for prematurely born infants.[1] While from a long-range point of view prevention of premature birth will probably be the more productive aspect, nevertheless better pediatric and nursing care must be provided for those infants born prematurely in the interim. A basic objective in most of the programs is the development of "premature centers" where specialized pediatric and nursing care will be available.[2] This paper, describing the desirable elements of a premature center, is based upon the experience of the New York City Department of Health in assisting hospitals to develop such centers.

FUNCTIONS OF THE PREMATURE CENTER

A premature center should perform several functions. 1. It should care for premature infants born in the hospital within which the premature center is located and also care for premature infants born in other hospitals or at home. Such care should be in accord with modern well-accepted standards of pediatric and nursing care for premature infants. 2. The center should give instruction to parents while the premature infant is still in the center. 3. It should assist the family in making a plan for and obtaining continued medical and nursing supervision of the infant after his discharge from the center. In addition to these basic functions, many premature centers also carry out the following additional activities: (1) maintain a follow-up clinic for health supervision of premature infants after discharge; (2) train physicians and nurses, and (3) perform research on prematurity.

From the Maternity and Newborn Division, New York City Department of Health.

1. Wallace, H. M.; Losty, M. A., and Wishik, S. M.: Prematurity as a Public Health Problem, Am. J. Pub. Health **40**:41-47 (Jan.) 1950. Chipman, S. S., and Treuting, W. L.: Louisiana's Program for the Care of the Premature Infant, Pediatrics **5**:45-51 (Jan.) 1950. Hardy, J. B.: Special Program Helps Premature Babies to Survive, Child. **11**:82-85 (Nov.) 1946. Taylor, E. S., and Gordon, H. H.: The Premature Infant Program in Colorado, Mother **10**:1-7 (Oct.) 1948. Marquis, H.: When a Premature Baby Is Born, Child. **14**:150-151 (April) 1950. Gordon, H. H.: Some Facets of the Colorado Premature-Infant Program, ibid. **14**:152-154 (April) 1950. Baumgartner, L.: The Program for Prematurely Born Infants in New York City, New York J. Med. **50**:289-293 (Feb. 1) 1950.

2. Recommended Standards for the Care of Premature Infants in New York City, Bureau of Child Hygiene, New York City Department of Health, 1948.

With these functions in mind, what should a premature center be expected to provide?

PEDIATRIC SUPERVISION

It is essential that a premature center be under the medical directorship of a qualified pediatrician who is especially interested and trained in the care of premature infants. The director and his staff should establish policies and procedures. The premature center should be under the direct supervision of a single attending pediatrician assigned for this sole purpose. The reasons for the assignment of the responsibility of the premature center to one attending pediatrician are several. First, this makes for continuity of pediatric supervision. Second, when there are differences of medical opinion, there is a designated pediatrician-in-charge to whom the problems may be taken for solution. Third, the supervising nurse of the center and the house staff have one member of the attending pediatric staff to whom they may present new ideas or problems. At least daily rounds should be made by the attending pediatrician so that established policies and procedures are carefully carried out.

Members of the pediatric staff of the hospital and other physicians should be encouraged to participate in the care of their own premature patients to provide continuity of medical care. Such participation should be in accord with the policies and procedures established by the pediatric director and staff of the premature center. In instances where other physicians participate in, or take charge of, the care of an infant or infants, the pediatric director or his designated attending pediatrician should have the final authority and responsibility when there is any difference of opinion.

In addition to qualified pediatricians on the attending staff, an adequate pediatric house staff should be provided so that 24-hour coverage of a skilled type will always be available. The first essential is a pediatric resident or assistant resident who, during his period of assignment, should have little or no contact with sick infants and children on the general pediatric service. At least one pediatric intern or rotating intern should be assigned to the center as well. During their assignments such house-staff members also should have little or no contact with sick infants and children. One practical method is to assign the resident and intern house-staff members to the newborn nursery service and to the premature follow-up clinic at the same time as assignment is made to the premature center.

It is desirable that periodic joint staff conferences, at least on a monthly basis, be held with members of the obstetric, pathology, and nursing staffs to review problems of mortality and morbidity and to evaluate the effectiveness of established policies and procedures.

NURSING STAFF

Just as there is a pediatric director of the premature center, so, too, there should be a nurse-in-charge. (Supervisor, charge nurse, etc., are the titles usually employed.) She should have had advanced training and/or experience in the care of premature infants in a recognized premature center. She should be responsible for the technical nursing policies and procedures and for the supervision of the center to see that these policies and procedures are carried out. In addition to the

nurse-in-charge, there should be a staff of at least four graduate nurses with training in the care of premature infants, so that each eight-hour tour of duty, including relief, is covered at all times by qualified nurses.

Recommended standards [3] suggest a general ratio of one member of the nursing staff for each four premature infants. However, the exact amount of nursing staff necessary will depend upon the weight-group distribution and general condition of the premature infants within the center. Obviously small and sick premature infants will need more nursing care, both quantitatively and qualitatively, than larger and well premature infants. The physical layout and equipment in the modernly designed premature centers and the proper allocation of functions to the various types of personnel may indicate a modification of the present recommended nursing standards. Such modification awaits further studies of nursing time.

Conclusions regarding the amount of professional nursing time necessary in contrast to the nonprofessional time (aides, attendants, practical nurses) also awaits further studies. At no time, should nonprofessional nurses work without the supervision of a professional nurse. Providing a ward clerk will relieve the nursing personnel of many clerical duties, such as charting weight and temperature and making out requisitions for supplies and equipment, and will therefore release nursing time for the care of premature infants.

Since premature infants need a maximum of skilled nursing care, such care should be provided at all times. Assignment of nursing personnel on a shared basis with other hospital services is not desirable. We believe that a completely separate nursing staff is needed. This point cannot be emphasized too strongly for two reasons: first, to provide skilled nursing care at all times, and second, to eliminate any possibility of interchange of nursing staff between the premature center and infected areas of the hospital.

PHYSICAL SETUP

The premature center should be planned as a separate integrated unit, located away from a sick or infected area of the hospital. The physical plan of a premature center might be subdivided functionally into several categories: (1) facilities for noninfected premature infants; (2) facilities for infectious and potentially infectious premature infants; (3) a teaching area; (4) work and accessory space; (5) a laboratory, and (6) dressing facilities for staff and visitors.

Facilities for Noninfected Premature Infants.—It is desirable for smaller premature infants that there be nursery rooms, each to contain not more than four infants; for larger premature infants, the nursery rooms might be designed to contain six. Each nursery room should have hot and cold running water, scale, and diaper and discard cans. An average of 30 sq. ft. (914 sq. cm.) per infant is recommended for each nursery room. All care to the infant should be on a completely individualized basis, so that there will be a minimum chance of cross infection; having equipment for each infant (linen, thermometer, etc.) at the cribside seems the most practical way of assuring safety to the infants. A separate bedside table

3. Dunham, E. C., and Crane, M. M.: Standards and Recommendations for Hospital Care of Newborn Infants, Bureau Publication 292, United States Department of Labor, Children's Bureau, 1943.

should be provided for each infant. Because oxygen is usually given routinely to all premature infants, at least for an initial period after birth, it is advantageous to have oxygen piped to each nursery room with an outlet for each infant's unit.

Air conditioning for infant care is an unsettled question among pediatricians. The necessity of air conditioning for safety is questioned where an adequate supply of efficient incubators is provided. If air conditioning is provided, at least one nursery room should be nonconditioned for the proper acclimatization of those infants near the time of discharge from the center. Our observations of those premature centers which have been established so far in New York City have been that a center without air conditioning is a very uncomfortable working environment for the staff. Working conditions are becoming more and more a factor in securing and retaining personnel.

TABLE 1.—*Facilities and Policies for Care of Suspect and Isolation Infants in Premature Centers in New York City*

	Provision in Premature Centers			
Center	Suspect Nursery	Isolation Nursery	Initial Period of Observation of Extramural Infants	Method of Handling Extramural Premature Infants
1	Yes	Yes	Yes, 48 hr.	After 48 hr. in suspect nursery, extramural infants mixed with intramural groups
2	No	No	No	Center set up to separate extramural and intramural infants; in practice, separation not completely carried out and two groups mixed immediately
3	No	No	No	Extramural infants completely separated from intramural group, except toward end of period of hospitalization
4	Yes	No	Yes, usually 48 hr.	After 48 hr. in suspect nursery, extramural infants mixed with intramural group; sometimes, extramural infants mixed immediately with intramural
5	No	No	No	Extramural infants usually admitted and cared for in separate room, but this not always followed; center does not admit extramural babies over 48 hr. old
6	Yes	Yes	Yes, 24-48 hr.	After 24-48 hr. extramural infants mixed with intramural

Each nursery should be provided with a sufficient number of electric outlets for the use of incubators, and for electric suction machines if desired; an electric outlet should be provided for each infant's unit.

A question frequently asked is the proportion of incubators and regular bassinets in a premature center. The final answer depends on several factors, the most important of which are (1) the birth weight distribution experience of the hospital in which the premature center is located, and (2) the portion of the center intended for premature infants born outside of the hospital, since this group is likely to be primarily composed of smaller infants. There appears to be no need for heated cribs, since modern incubators have all the advantages of heated cribs and are able to serve an additional purpose of supplying a higher concentration of oxygen. In addition, most incubators are less expensive than most heated cribs.

Facilities for Infectious and Potentially Infectious Premature Infants.—There has been no complete agreement to date on the necessity of providing facilities within the premature center for infectious and/or potentially infectious premature infants. The variation in opinion is illustrated in Table 1, showing the present method of handling such cases in the six approved premature centers in New York City. Only three of the six centers have a suspect nursery within the premature

center. Where a suspect nursery is provided within the center, the initial period of segregation of extramural premature infants is usually 48 hours. In none of the six centers is there complete separation of all extramural premature infants from all intramural premature infants during the entire period of stay in the center.

Likewise, there is variation in facilities for the isolation of premature infants with a diagnosis of definite infection. Only two of the six premature centers have an isolation nursery within the premature center. When a premature infant needs to be isolated in those centers not having an isolation nursery, one of two types of arrangement exists: (1) The infant may be removed to the general pediatric service. The obvious disadvantage in this method is that the infant may contract an entirely different infection in addition to the one he already has. (2) The nursery room in which the infected infant is being cared for in the premature center is

TABLE 2.—*Nursing Staff Caring for Suspect and Isolation Infants in Premature Centers*

	Suspect Infants		Isolation Infants	
Center	In Centers With Suspect Nursery	In Centers Without Suspect Nursery	In Centers With Isolation Nursery	In Centers Without Isolation Nursery
1	Same staff for suspect and normal infants	.....	Same staff for suspect and normal infants	.....
2	.....	Same staff for suspect and normal infants	.....	If infected baby, room is closed; not always possible to assign separate staff although policy calls for it
3	.....	Nursery with suspected case closed; separate staff	.....	Diagnosed infection transferred to pediatrics and cared for by regular pediatric nursing staff
4	Same staff for suspect and normal infants	.....	.....	Infected infants cared for in suspect nursery (other suspect infants moved out); separate nurse assigned
5	.....	Same staff for suspect and normal infants	.....	Infected infants cared for in pediatrics by regular pediatric nursing staff
6	Same staff for suspect and normal infants	.....	.....	Same staff for normal and isolated infants

treated as an isolation nursery and is closed to further admissions. The obvious disadvantage in this method is the continuing exposure of other infants stationed within this nursery room to the one infectious infant.

Of equal importance is the assignment of nursing staff caring for suspect and isolation premature infants. In five of the six centers in New York City, the same nursing staff within the premature center cares for both suspect and "clean" premature infants; in the sixth center a separate staff is assigned. There is more variation in the method of caring for isolation infants: In three centers the same nursing staff cares for both clean and isolation infants; in two centers, the infected infant is transferred to the pediatric service and is cared for by the regular pediatric nursing staff; in one center, the infected infant is cared for in the suspect nursery of the premature center by a separate nursing staff (Table 2).

Our general opinion, from a conservative point of view, is that it is safer to provide both a suspect and an isolation nursery within a premature center. With the wide variation in handling these categories of patients, as is seen in Tables 1 and 2, only time and experience will demonstrate whether this opinion is substantiated.

The Teaching Area.—Because the period of hospitalization of a premature infant may be relatively long, there is sometimes a long period when he is separated from his parents. This separation alone creates anxiety and insecurity on the part of the parents. Other reasons for this parental reaction are (1) the very fact that the infant is born prematurely and (2) that he may have special problems even when he attains a weight of 5 or 5½ lb. (2,300 or 2,500 gm.). One of the functions of the premature center is to allay this feeling of anxiety and insecurity by a program of parental instruction toward the end of the period of hospitalization. Such a program entails qualified and interested pediatric and nursing staff, teaching equipment, and a room within the premature center where such instruction may be carried out. In the last week or two weeks of the infant's stay in the center, he is brought to the teaching room. Here the parent or parents become acquainted with their infant, learn how to feed, diaper, and hold him, and the mother may be taught the method of breast milk expression or formula preparation. The teaching room should therefore have at its entrance washing and dressing facilities for the use of parents in handwashing and donning a cap, gown, and mask, for the care of teaching equipment, and for the actual parental instruction and participation in care. In the broad concept of the functions of the premature center, the teaching program for parents is a necessity, if the center is to play its potential role in the community.

Such a teaching program rightfully is the responsibility of the attending pediatrician, the resident pediatrician assigned to the premature center, and the supervising nurse. In initiating the teaching program, it is advisable to carry on the instruction of parents on an individual basis; more experience is needed for group instruction of parents of premature infants.

Work and Accessory Space.—It is important to have a clean workroom, an unclean workroom (general utility room), a chart room or area, and a space for storage. Two types of workrooms are considered necessary.

The functions of the clean workroom are as follows: storage of formulae which have been prepared in the general formula room of the hospital; preparation and storage of special medications and therapeutic equipment; storage of sterile supplies, such as intravenous equipment; preparation and storage of feeding equipment, such as gavage sets, droppers, and clean supplies for general care of infants, and preparation for the administration of vitamin supplements. The clean workroom should contain a work table, sterilizer, refrigerator, sink, and storage cabinets.

The unclean workroom is the area where the used equipment and supplies of the center are taken for dismantling and cleaning. This applies to the handling of such material as the incubator, bassinet, and other equipment when no longer used by an infant, and to the cleaning of gavage and intravenous sets. The unclean workroom should contain a work table, sterilizer, sink, discard containers, and storage cabinet.

A chart room or area is necessary for the charting of pertinent data on permanent records of the infants and for review of such records by the pediatric and nursing staffs. Such a room or area should be located near the main entrance to the premature center for easy access to the attending pediatric staff and to outside physicians who may wish to review individual records.

Ample storage facilities within the unit must be provided for the storage of extra linens, supplies, records, forms, and oxygen tanks if central piping of oxygen is not used.

Dressing Facilities.—In addition to the dressing facilities described above for the teaching area, dressing and scrub facilities are necessary for physicians and for nurses. For physicians these should be located at the entrance of the unit and should consist of a scrub sink and a cabinet containing a supply of masks and gowns. Likewise there should be a place where physicians may hang their outer clothing.

Dressing facilities for nurses should be near the entrance to the unit and should consist of a room where the nursing staff of the unit may change from outer garments or regular uniform to the clothing specified by the premature center. Toilet facilities should be provided, so that the assigned nursing staff will not have to leave the unit.

Laboratory Facilities.—Obviously laboratory facilities should be available within the hospital for the care of premature infants, as for all types of hospital patients. While these facilities are usually a part of the hospital within which the premature center is located, in some hospitals, where considerable research on premature infants is carried on, the laboratory facilities may be a part of or near the premature unit. Provision is necessary in the hospital for doing blood counts, Rh determination, blood typing, and cross matching, as well as routine bacteriologic and biochemical tests.

A qualified hematologist or pathologist should serve as director of the hospital's general laboratory service and supervisor of the general laboratory work. Trained technicians to perform necessary laboratory determinations should be provided at all times.

SIZE OF A PREMATURE CENTER

No authoritative data exist on the minimum capacity of a premature center, nor is there any factual evidence regarding the maximum capacity beyond which there may be difficulties in administration and management. Experience has led us to believe that a capacity ranging from 20 to 50 infants per center may be administratively feasible and practical.

In regard to minimum capacity, there are two factors of importance: space and nursing personnel. If desirable standards are to be met, it is very expensive for a hospital to plan a center for 8 or 10 premature infants, because so much space is necessary for all of the accessory facilities and work space. In a small unit, a fluctuation in census of two or three infants is of major significance, and the immediate tendency is to withdraw the nursing staff of the center to other areas of the hospital. Furthermore, a minimum volume of patients is necessary for the clinical teaching of medical and nursing students and personnel.

POLICIES AND PROCEDURES

As stated previously, the pediatric director with his staff and the nurse-in-charge of the premature center should jointly establish the necessary policies and procedures for the care of premature infants within the center. In order that the total personnel concerned with the care of the premature infants may have a full understanding, it is desirable that such policies and procedures be written and incorporated into a manual,[4] which would include such major items as admission of a new

4. Suggested Work Manual for Premature Centers, New York City Department of Health, 1950.

infant to the center, emergency standing orders, relationship with the delivery room unit, feeding, maintenance of heat and respiration, the teaching of parents, plan for investigation of home conditions, plan for ongoing medical and nursing supervision, and a continuing plan for recording and statistical evaluation of the care of premature infants within the hospital.

RELATIONSHIP WITH THE DELIVERY ROOM UNIT

The responsibility of the premature center should begin with the care of the premature infant in the delivery room of the hospital of which the center is part. This responsibility would include the provision of a modern efficient incubator in each delivery room, resuscitation equipment and oxygen, and personnel trained in the use of such equipment. Policies for the use of such materials as vitamin K for both mother and infant should be established jointly by the pediatric director of the premature center and the obstetric staff. It is desirable that a member of the pediatric house staff assigned to the premature center be present at all deliveries in which the birth of a premature infant is anticipated. Provision should be made for the safe transportation of the infant from the delivery room to the premature center, so that heat and oxygen will be provided in transit.

The role of the obstetrician in the prevention of premature birth and in safeguarding the baby when the mother is in premature labor has been well described by Beck [5] and Taylor.[6]

RELATIONSHIP WITH OPHTHALMOLOGY DEPARTMENT

Because retrolental fibroplasia develops almost exclusively in premature infants, the period of hospitalization presents an excellent opportunity for case finding. Many premature centers have therefore established an arrangement with the hospital ophthalmologic service for weekly eye examination of all premature infants. Wider adoption of this policy in all premature centers might give an explanation for the apparent differences in the incidence of retrolental fibroplasia in different geographic areas as well as in different hospitals in the same area. It is obvious that such a policy would mean earlier finding of cases, earlier attempts at therapy, earlier preparation of the family, and an earlier plan made for the child's handicap.

HOME FOLLOW-UP PROGRAM AND ONGOING MEDICAL SUPERVISION

The responsibility of the premature center does not end when the infant is discharged from the center. A plan should be made to assure the personnel of the center that the home is suitable and that the parents are prepared to receive the infant. For example, it may occasionally happen that the infant is discharged when other family members have an infectious condition. All the center's medical and nursing care may be useless if at home the infant contracts an infection serious enough to warrant rehospitalization. In other instances, the home may have no heat provided even in very cold weather, or provision may not yet have been made for the infant's clothing, bathing, sleeping, etc.

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5. Beck, A. C.: How Can the Obstetrician Aid in Reducing the Mortality of Prematurely Born Infants? Am. J. Obst. & Gynec. **42**:355-364 (Aug.) 1941.

6. Taylor, E. S.; Phalen, J. R., and Dyer, H. L.: Effect of Obstetric Difficulties and Maternal Disease on Premature Infant Mortality, J. A. M. A. **141**:904-908 Nov. 26) 1949.

The best method to obviate the above problems, with their potentially serious consequences, is an arrangement with the community nursing agency [7] whereby home visits are made before the expected date of the infant's discharge, home conditions are reported back to the center, discharge decision is based on the report of home conditions, and a subsequent home visit made within 24 hours after discharge.

The center also has the responsibility for assisting the family in making a plan for continuing medical supervision, whether by a private physician, community or hospital well-baby clinic, or special follow-up clinic for premature infants maintained by the center.

SOCIAL SERVICE

In the broad concept of the functions of a premature center, the social worker has an important role in (1) assisting the family in meeting the high costs of hospital care, (2) helping the family to plan for a handicapped child, and giving (3) assistance in the home follow-up program. In regard to the last-mentioned function, the prompt discharge of the infant depends many times on whether there is a family or social problem at home. Here the social worker's guidance is needed. When such home problems are not recognized early, the result may be that the infant needs to be hospitalized after he is physically ready for discharge, thus depriving another premature infant of a place in the center. For example, some premature infants are delivered of unwed mothers or come from broken homes. In some of these instances, infants do not have homes to which they may be discharged. For them a plan must be made for proper placement in foster homes or children's shelters, prior to the establishment of a long-range plan for infant and mother.

RECORDS

The premature infant's record should contain at least two types of essential data: (1) information regarding the mother and (2) information regarding the clinical course of the infant in the center. Pertinent data on the mother should include her antepartum course, labor and delivery, including Rh status, analgesia, anesthesia, complications, length of labor, and type of delivery. The data on the clinical record of the premature infant should begin with the condition and care in the delivery room, admission, periodic and discharge physical examinations, progress notes, pediatrician's orders, treatments given, and indicated laboratory data. Nurses' progress notes should give a clear description of respiration, methods of and reactions to feeding, daily inspection of the infant, and the number and type of stools. The infant's record should contain the report of home conditions as ascertained by the public health nurse, and the plan for future medical supervision after discharge from the center.

It is recommended that a simple type of daily worksheet be used for each nursery room. Such a worksheet should contain the following types of data: names of infants in each room, weight, temperature, stools, amount of feeding taken and reactions to feeding, medications and treatment, and unusual symptoms observed by the nurse. Such data should then be transferred daily to the hospital record of the individual infant.

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7. Plan for Home Followup of Premature Infants, Administrative Order 39, New York City Department of Hospitals, Dec. 1948.

STATISTICAL EVALUATION

One of the first questions usually asked by visitors to a premature center is "What sort of statistics are you keeping and what do they show?" In order to answer the visitors' question and in order to evaluate the care given by the hospital to premature infants, mortality statistics should be kept on a continuing basis.[8] Such statistics should begin with the birth of the infant in the delivery room and include the entire hospital life of the premature infant for his neonatal and early postneonatal periods. It is usually considered sound to separate the statistics into the following groups: (1) intramural and extramural, (2) white and nonwhite, (3) birth-weight groups (1,000 gm. or less, 1,001 to 1,500 gm., 1,501 to 2,000 gm., and 2,001 to 2,500 gm.), and (4) time intervals, such as first 24 hours of life, second 24 hours of life, rest of first week, and thereafter.

TABLE 3.—*Cost of Construction and Equipment of Premature Centers in New York City in 1949 to 1951*

Center	Capacity	Total Cost			Cost per Bassinet		
		Total	Construction	Equipment	Total	Construction	Equipment
New Construction in a New Building							
A	46	$331,992	$279,676	$ 52,226	$7,215	$6,082	$1,135
B	30	105,396	91,632	13,764	3,513	3,054	459
Complete Reconstruction in an Existing Building							
C	20	$ 99,971	$ 74,971	$ 25,000	$4,999	$3,748	$1,250
D	32	71,221	52,323	18,898	2,226	1,635	591
E	32	67,931	51,067	16,869	2,123	1,596	527
Partial Reconstruction in an Existing Building							
F	50	$ 91,900	$ 57,658	$ 34,242	$1,838	$1,153	$ 685
G	23	27,744	16,484	11,260	1,206	717	489
H	16	20,200	11,820	8,380	1,262	739	524
Expansion of an Existing Premature Center							
I	42	$ 31,725	$ 17,464	$ 14,261	$ 755	$ 416	$ 339
Totals	291	$847,900	$653,090	$194,900	$2,914	$2,244	$ 670

RELATIONSHIP WITH THE PATHOLOGY DEPARTMENT

It is clear that there is much valuable information to be gained by the study of the death of an individual infant. The amount of information depends to a great extent on the performance of the postmortem examination by a pathologist with special interest and training in neonatal pathology. It is important that there be a close working relationship between the members of the pediatric, obstetric, and pathology departments of the hospital, so that there may be retrospective study and correlation of the clinical course of mother and infant with the findings presented at postmortem examination.

COSTS IN PREMATURE CENTERS

There is no question that the construction, equipment, and proper operation of a premature center are costly. Table 3 presents a picture of the cost of construction and equipment of those premature centers in New York City which have applied for federal funds.

8. Wallace, H. M.; Mindlin, R. L.; Lenz, A., and Rich, H.: Methods of Securing Uniformity in Hospital Statistics on Premature Infants in New York City, J. Pediat. **39**:200 (Aug.) 1951.

Data on the cost per bassinet in the centers have been grouped in categories, according to the amount of original physical facilities previously provided and, therefore, of the new construction necessary. Total cost per bassinet varies from $7,215 in completely new construction to $755 in a center which was expanded in capacity. One additional factor in cost illustrated in Table 3 is the provision of air conditioning in Centers A, B, and C.

Even more costly than the initial construction and equipment is the long-range operation of the center. Studies in New York City indicate that the cost per infant cared for in a premature center according to standards is approximately $18 per day. The predominant factors contributing to this high cost are nursing and auxiliary staff, oxygen, blood, and expensive drugs. It is for this reason that the New York City Department of Health, like that in many other communities, is now paying for the care of premature infants in approved premature centers.

SUMMARY

This report presents some of the factors which our experience in New York City has shown to be necessary for the development of centers for the specialized care of premature infants. Such elements have been described as the functions, pediatric supervision, nursing staff, physical setup, size, policies and procedures, relationship with the delivery room unit, plans for home follow-up and ongoing medical supervision, statistical evaluation, and relationship with ophthalmology and pathology departments.

125 Worth St. (13).

News and Comment

ANNOUNCEMENTS

Refresher Course in Pediatrics.—The central theme of this year's regular refresher course for pediatricians at Tulane University of Louisiana, New Orleans, Feb. 11 through 16, will be "Accidents." Visiting faculty members for the course will include Dr. George Wheatley, New York, Dr. Albert D. Kaiser, Rochester, N. Y., and Dr. Irvin Kerland, Washington, D. C. Major emphasis will be paid to defining the pediatrician's role in community planning for prevention and management.

Those interested should communicate directly with the Department of Pediatrics or the Division of Graduate Medicine, Tulane Medical School, 1430 Tulane Ave., New Orleans.

Society Transactions

SOCIETY FOR PEDIATRIC RESEARCH

Harry H. Gordon, M.D., *President*

Twenty-First Annual Meeting, Atlantic City, N. J., May 2 and 3, 1951

First Session

Wednesday Morning, May 2

Isolation of a Virus (Not Previously Described) Causing Encephalitis in Mice. Dr. Horace L. Hodes, Helen D. Zepp (by invitation), and Dr. Alfred L. Florman, New York.

In February, 1948, an outbreak of diarrhea involving eight infants occurred in the newborn nursery of the Johns Hopkins Hospital. Stools from two infants were stored in the frozen state until October, 1950. They were then pooled, rendered free of bacteria with antibiotics, and injected subcutaneously into eight litters of mice 1 to 3 days old (61 mice). At the end of seven days, although no illness was noted, the bodies of 16 of these mice were pooled, rendered sterile with antibiotics, and injected subcutaneously into 19 suckling mice. At the end of six days one of these mice showed paralysis of both hindlegs. Passage of the body of material from this animal as well as from a pool of four of his experiment mates resulted in the production of paralysis and convulsions in seven of 49 suckling mice. With each subsequent passage the percentage of affected mice increased rapidly, and since the seventh passage intracerebral or intra-abdominal injection of brain of affected mice has produced generalized convulsions and death in 100% of suckling mice. The disease produced in mice is characterized by sudden, extremely violent tonic and clonic convulsions involving the entire body. Paralyses are seen occasionally but are not present in most animals. Mice showing definite symptoms always die. Over 20 successive passages have been accomplished.

The self-perpetuating agent responsible for the above findings is clearly a virus. It passes readily through a Seitz filter, and cultures of inoculated material have been free of bacteria. In mice 1 to 5 days old the virus produces fatal encephalitis in intracerebral, intra-abdominal, or subcutaneous injection. The incubation period following intracerebral injection into suckling mice is two days, with most animals dead in 72 hours. Mice 10 days of age are uniformly susceptible; the same is true for mice 17 days of age when inoculated intracerebrally. Passage in 17-day-old mice is readily accomplished. However, intracerebral inoculation of mice 4 weeks old or more causes no apparent disease, and all such mice survive. The virus has produced paralyses in only seven of 248 suckling hamsters and two of 29 suckling guinea pigs.

In suckling mice virus is found in relatively large amounts in brain and cord ($LD_{50} = 10^{-5.5}$ to $10^{-6.5}$), but none is detectable in the skeletal muscles.

Pathological findings have been limited to the central nervous system. Meningeal infiltration, perivascular cuffing, areas of necrosis, neuronal injury, and neuronophagia are found throughout the central nervous system. No lesions are found in skeletal muscle, heart, liver, pancreas, or interscapular fat pads. No inclusion bodies have been found.

The new virus differs from the viruses of the Col. SK group by the fact that the latter produce paralysis, not convulsions; their effectiveness is not limited to mice under 4 weeks of age; they produce muscle lesions after intra-abdominal injection into suckling mice. Col. SK virus is very effective in hamsters; the new virus produces diseases in only a very small percentage of suckling hamsters. The Col. SK group agglutinate sheep red cells, the new virus does not. The new virus is not neutralized by hyperimmune monkey serum, which neutralized SK virus.

The new virus differs from viruses of the Theiler group in that the latter affect mice over 4 weeks of age when injected intracerebrally. While one strain of the Theiler group (GDVII) may produce convulsions after intracerebral injection, it does not do so when injected intra-abdominally, even in suckling mice. GDVII virus agglutinates human type O red cells; the new virus does not. Hyperimmune GDVII mouse serum does not neutralize the new virus.

The effectiveness of the Coxsackie group of viruses, like the new virus, is limited to very young mice. There are a number of differences between the two viruses, however. Some strains of Coxsackie virus may produce paralysis in 17-day-old mice, but they cannot be regularly passaged in mice of this age. Passage of the new virus is readily accomplished in 17-day-old mice. Generalized convulsion is the rule with the new virus, flaccid paralysis with Coxsackie virus. Virus is not present in the muscles of animals infected with the new virus, but Coxsackie virus is uniformly present in the muscles of mice infected with it. The lesions produced in muscles, fat pads, liver, and pancreas by Coxsackie virus are not seen with the new virus. Suckling hamsters are susceptible to infection with Coxsackie virus, but the new virus has produced disease in only 3% of suckling hamsters inoculated.

According to Melnick, all strains of Coxsackie virus are effectively neutralized by gamma globulin. The lots of gamma globulin used by Melnick, as well as gamma globulin from two other sources, have failed to neutralize the new virus.

Sera of normal mice of the stock used in these experiments have shown no neutralizing action. Sera obtained during the acute and convalescent stage from the two infants whose stools were used as the original inoculum in these experiments were lost, and therefore they were not tested against the new virus. Sera obtained three years after their illness from three nursery mates of the two infants referred to above have failed to show significant neutralizing action against the new virus. Further work with sera from infants suffering from diarrhea is under way and will be extended.

In conclusion, a virus which has apparently not been described before has been isolated. Whether its source is from human beings or from mice remains to be determined.

DISCUSSION

DR. H. A. WENNER, Kansas City, Kan.: I wanted to ask whether you had gone back to these six babies and taken serum to determine whether there was neutralization of the virus or not.

DR. HORACE L. HODES, New York: I am afraid I rushed over the last part of the paper. We obtained serum three years later from some of the children. We were unable to obtain serum from the children whose stools were used in these experiments; however, we did get serum from three of their nursery mates who had also been sick, three years after the original illness. We were not able to illustrate very much in the way of neutralizing antibodies in these sera.

Rubella Without Rash: A Phenomenon Observed During Studies on Immunization.

DR. SAUL KRUGMAN and DR. ROBERT WARD, New York.

Nasopharyngeal washings and blood were obtained from a patient 13 hours after the appearance of a rash characteristic of rubella. Subinoculation of these bacteria-free materials in human subjects resulted in typical rubella in two, while in two others transitory illnesses developed which were suggestive of rubella without rash. Blood from one of the latter patients was injected intramuscularly into another subject in whom rubella with typical rash developed. The original agent has been transferred successfully through two passages in human subjects. Incubation periods varied from 12 to 16 days, the majority being 13 days. In two adults typical rubella developed after natural exposure to subjects with the experimental disease. Attempts to transfer the agent to cynomolgus monkeys and to chick embryos have been unsuccessful. The agent was preserved for nine months frozen in the solid carbon dioxide chest. In general, these observations confirm and extend the Australian studies carried out by Anderson (Experimental Rubella in Human Volunteers, *J. Immunol.* **62**:29, 1949) and point the way toward a possible immunization program as a public health measure.

DISCUSSION

DR. HERBERT C. MILLER, Kansas City, Kan.: I think it is pertient to add a little gray to this black-and-white presentation that we have just had. I think it would be a fair guess that rubella is probably the most important acute infectious disease so far as its permanent effects on the organism are concerned. I think all of us have had the experience of seeing cases in which

the baby has the so-called rubella syndrome and there is no history of rubella in the mother. In my experience, the history of rubella in the mother has been lacking as many times as it has been present, and perhaps this very significant work that Dr. Krugman and Dr. Ward have done gives us further clues for thinking that these babies with the rubella syndrome, when there has been no rash in the mother, may be part of the total picture.

DR. ALEX J. STEIGMAN, Louisville: I should like to ask whether there has been opportunity to challenge any of the human recipients who showed either minor illness or the one incident of complete escape. This bears on the question of the solidity of immunity and on the question of types of rubella virus.

DR. SAUL KRUGMAN, New York: We have not had that opportunity, Dr. Steigman.

I want to thank Dr. Miller for his comments. He has highlighted an important point. The question of whether rubella without rash can conceivably cause malformations in the newborn infant as well as rubella with rash is one that remains to be answered. It is extremely important to emphasize that the experimental disease is contagious and that any widespread immunization attempts might therefore produce rubella in the pregnant mother as well as in the child; consequently, if immunization procedures of this type are contemplated at any future date, isolation will have to be practiced.

Studies on the Berry-Dedrick Transformation of Fibroma. DR. MARGARET H. D. SMITH, New Orleans.

The experiments of Griffith in 1928 on transformation of pneumococcic types led to the well-known studies of Avery and his group, as well as to investigations by Boivin, by McKenzie, and by Hattie Alexander on transformation of colon bacilli, Salmonella, and Hemophilus influenzae respectively. Less well known, however, are the experiments of Berry and Dedrick, who, in 1935 and 1936, were successful in bringing about a similar transformation in the domain of viruses. They carried out studies on the fibroma virus, which gives rise to a benign, non-contagious, tumor-like condition of rabbits, and myxoma, a highly malignant, contagious virus infection of rabbits. They were able to show that fibroma virus, when mixed with a heat-inactivated extract of myxoma, was itself transformed into myxoma virus. Several investigators have confirmed the observations of Berry and Dedrick but have found this transformation to be only irregularly reproducible.

Our own investigations have amply confirmed this observation. We have, however, been able to show that it occurs more readily with some strains of fibroma virus than with others, and that transformation is a stepwise phenomenon, so that the tumor-producing properties of fibroma virus can be enhanced at will. The transformation can be brought about using either a crude transforming agent or one which has been deproteinized.

These studies show that the constitution of viruses and cells, as well as the constitution of bacteria, are controlled genetically by substances which are not protein in nature.

DISCUSSION

DR. HATTIE ALEXANDER, New York: I think Dr. Smith's work represents a very important contribution. It certainly will prove of interest to the microbiologists as an additional example of a reproducible method of inducing change in inherited characteristics; and also it is of interest because it supports the speculation that these transforming principles may play an important role in epidemics and may explain the origin of species of micro-organisms. But I think of greater importance than either of these is the fact that it offers another tool, a reproducible one, for exploring the nature of this substance and also its mechanism of action, with the end in view of eventually being able to change the genetically determined abnormal functions of cells of higher species.

As you know, in the two bacterial systems of H. influenzae and pneumococcus, the transforming substance has been fairly well defined. I think all the data support the view that the transforming principle is a pure desoxyribonucleic acid, and I wonder if Dr. Smith has examined her material containing the transforming principle for the presence of desoxyribonucleic acid.

While the two systems have been shown to have a transforming principle with similar chemical characteristics, the mode of action data, at least in the studies done so far, suggest

different conclusions. You remember McCarty, Avery, and others have suggested from their data that, in the pneumococcus system, growth in a very complex environment is needed over a period of a few hours in order to do what they term "sensitize" the cells so that they are susceptible to the actions of the desoxyribonucleic acid. In our work with H. influenzae we have not been able to demonstrate similar requirements. I think it may be of interest to you to know that in this system our data suggest that the cells in the population which are susceptible to transformation rise by mutation, and they make up a very minute proportion of the whole of any so-called susceptible strain. When a population which is known to contain these susceptible cells is exposed to an active transforming principle, the change in the inherited characteristics takes place virtually immediately.

Moreover, I believe our data show that the process which takes place immediately is apparently completed within a period of 15 minutes in an environment which does not contain the various complex substances reported to be necessary in the pneumococcus system or substances which will support growth.

Isolation and Typing of Poliomyelitis Viruses in Tissue Cultures. Dr. F. C. Robbins, J. F. Enders, Ph.D. (by invitation), and Dr. T. H. Weller (by invitation), Boston.

The cultivation of poliomyelitis viruses in cultures of human tissues has been previously reported. It has been shown that these agents destroy tissue cells in flask and roll-tube cultures and that this destruction is inhibited by specific immune serum. Tissue destruction provides a criterion by which virus growth can be detected and its antigenic type determined without animal inoculation.

In this communication the isolation of poliomyelitis virus from patients by inoculating stool and spinal cord suspensions containing penicillin and streptomycin into flask cultures of mature human kidney or human embryonic tissue is described. The viruses thus isolated have been typed in roll-tube cultures of human embryonic or of mature uterine tissue.

A virus was isolated from the stool of each of nine paralytic patients tested and from the spinal cord of a patient who died. Agents were also obtained from the stools of five of six patients with nonparalytic poliomyelitis. Three of these agents were shown to be poliomyelitis viruses, while two produced a cytopathogenic effect but have not yet been identified. Of the last two agents, one has been injected into a monkey and produced no disease. Virus was not isolated from the stools in five cases resembling nonparalytic poliomyelitis but in which this diagnosis was not subsequently supported. Moreover, viruses were not obtained from the brain and cord in a case of sporadic encephalitis, nor from the blood in a case of fatal poliomyelitis.

Thirteen of the poliomyelitis strains have been typed, three as Brunhilde and 10 as Leon. Two viruses were isolated in 1949; both were Brunhilde type. In 1950 one Brunhilde and 10 Leon strains were isolated. This finding suggests that the Leon type of poliomyelitis virus was predominant in the Boston area in 1950.

The possible advantages of these procedures for the isolation of poliomyelitis viruses and the determination of their serologic type are discussed.

Coxsackie and Poliomyelitis Viruses in Paralytic Poliomyelitis. Dr. E. C. Curnen and Dr. J. L. Melnick (by invitation), New Haven, Conn.

The Coxsackie viruses are recently discovered filtrable agents of small particle size characterized chiefly by their capacity to cause fatal disease and destructive lesions of striated muscles in newborn but not weaned mice and hamsters. These viruses have been recovered from children and adults with illnesses resembling poliomyelitis or aseptic meningitis, epidemic myalgia or pleurodynia (Bornholm disease), influenza or herpangina and from others in whom clinical evidence of disease was mild and not distinctive or absent. At least 10 types have been distinguished by immunological methods. These viruses appear to be widely distributed in nature, but the relative incidence of infection by the different individual types, the frequency with which they cause human disease, and the incidence of various forms of illness induced by them have not been determined.

Specimens of feces from 20 children suspected of having poliomyelitis, who were hospitalized in New York City during the epidemic of poliomyelitis in 1949, were tested in infant mice for the presence of Coxsackie viruses. From two girls with paralysis (Patients 5 and 10) strains

of virus which caused fatal paralysis of infant mice were recovered and identified as Coxsackie viruses (Dalldorf I). From both patients strains of poliomyelitis virus which produced paralytic disease and lesions typical of poliomyelitis after intracerebral injection in monkeys were also recovered. The latter strains were not pathogenic for infant mice. Neutralizing antibodies against the homologous strains of Coxsackie virus were found in both patients but rose to high titer in only one (Patient 10).

Although Coxsackie and poliomyelitis viruses have certain properties in common, they differ in several respects, particularly in pathogenicity, antigenicity, and host range. Nevertheless, it seemed possible that some strains of these two agents, particularly those isolated from the same patient, might be related to each other. To investigate this possibility, cross neutralization tests were carried out in mice and monkeys with heterologous and homologous antisera and the strains of Coxsackie and poliomyelitis viruses which were found together in the feces of Patient 10. The results indicated that these viruses, which were both recovered from the same source, were not antigenically related to each other and provided additional evidence that the two viruses were different agents.

From the results of attempts made in our laboratories to recover Coxsackie viruses from individual patients suspected of having poliomyelitis in 1948, 1949, and 1950, the incidence of infection with Coxsackie virus and of paralysis in these patients did not appear to be related. A review of 29 instances in which both Coxsackie and poliomyelitis viruses were found together in the same patient revealed that concurrent infection with these viruses may be common at times when both agents are prevalent and suggested that flaccid paralysis in patients from whom Coxsackie virus has been recovered may be attributable to associated poliomyelitis virus. It has not yet been shown that a Coxsackie virus alone can induce paralytic disease in man nor to what extent infection by a Coxsackie virus may influence the course of disease in a patient infected at the same time by a poliomyelitis virus.

On the basis of present knowledge, it seems reasonable for the clinician or the epidemiologist to consider paralytic illnesses as poliomyelitis until convincing evidence to the contrary is made available.

Human Gamma Globulin in the Protection of Tonsillectomized Cynomolgus Monkeys with Experimental Poliomyelitis. Dr. John M. Adams, Dr. C. M. Carpenter (by invitation), Dr. J. D. French (by invitation), Dr. J. J. Pressman (by invitation), Dr. John L. Smith (by invitation), and S. J. Klein, Ph.D. (by invitation), Los Angeles.

There is increasing evidence that the viruses of poliomyelitis are capable of producing widespread infection in humans, particularly at times of epidemics. The paralytic forms of the disease are probably rare manifestations. It has been recognized for some time that the severe types of poliomyelitis may be associated with situations of stress such as pregnancy, undue exercise, inoculations, and operations.

Von Magnus and Melnick showed that tonsillectomized cynomolgus monkeys are more susceptible to infection after being fed poliomyelitis virus than are nontonsillectomized animals. Bodian demonstrated that the neutralizing potency of concentrated human gamma globulin was high against representatives of three distinct antigenic types of poliomyelitis virus.

In the first experiment, 22 monkeys were tonsillectomized, 11 were given 1 cc. of concentrated human gamma globulin for each pound (0.5 kg.) of weight intramuscularly, and all the animals were then fed Y-SK virus, approximately 100 $P.O._{50}$ (median paralyzing dose) a day for seven days.

The average temperatures ranged from 99.3 F. to 102.8 F., and during the height of the illnesses the animals which had not received gamma globulin had higher fevers. In two animals of the 10 in the treated group marked paralysis developed; two additional animals showed questionable weaknesses and fever; six remained well. In the untreated group, in three animals marked paralysis developed; two appeared to have symptoms of bulbar involvement; three animals were considered to have moderate involvement, and four animals had questionable weaknesses of a temporary character. One animal remained well. The histopathologic lesions were typical of experimental poliomyelitis, with perivascular and round-cell infiltration and neuronophagia with destruction of neurons. Two animals in the treated group and three in the untreated group were positive for poliomyelitis.

Acute and convalescent blood specimens were drawn and are being tested against the rodent-adapted strain of Y-SK virus used in this experiment. A few of the sera from the surviving animals in the treated group have been tested against a homotypic strain and were found to have antibodies present in the convalescent specimens.

In the second experiment, 24 animals were tonsillectomized and 20 animals served as controls. Twelve of the tonsillectomized animals were given 1 cc. of concentrated human gamma globulin for each pound of weight on the day of operation and 1 cc. for each pound three days later. Virus was again fed for seven days, as previously.

It is too early to include the final results here, but after 16 days there were three paralyzed monkeys in the treated group and three or four with involvement in the untreated group of tonsillectomized animals. No pathological studies are available as yet. Among the control animals no evidence of definite paralysis has been observed, but two monkeys are doing poorly, with generalized weaknesses. Bleedings are being done on all of these animals.

It is clear that under the conditions of this experiment there is no significant difference between the treated and untreated animals which were tonsillectomized and fed virus. The dose of virus in experimental poliomyelitis may be of such magnitude that gamma globulin given parenterally in doses of 1 cc. and 2 cc. for each pound is not sufficient to modify the experimental disease. There appears to be a significant difference in the paralytic-attack rate between tonsillectomized animals and animals not operated on.

DISCUSSION

Dr. C. Henry Kempe, San Francisco: The most crucial test of the effectiveness of a typing method in the field of poliomyelitis would seem to be the blind typing of unknown specific serum samples, and I should like to hear Dr. Robbins comment on his experience in doing so.

I should like to add that the substitution of tissue culture techniques for the traditionally used monkeys constitutes what seems to me the most important single contribution of many years to this field. Work here may consequently become much less costly. The experiments Dr. Robbins described with tissue cultures would, had he used monkeys, cost over $20,000 conservatively estimated, in terms of their purchase and care. If this method is a good one for the primary isolation and identification of the Coxsackie and poliomyelitis groups of viruses, a much more adequate study of them may be anticipated.

Dr. F. C. Robbins, Boston: Dr. Kempe has visited our laboratory and I think had something in mind when he asked this question. We have done blindfold tests on immune sera which were supplied us through the courtesy of Dr. Salk, of Pittsburgh, and although this is the reverse of what we have described, which has been the typing of virus strains, the system is exactly the same. We typed, all together, 14 sera, which included those containing antibodies against the three different types of poliomyelitis and also one serum which contained no antibody against poliomyelitis, and in each instance our results agreed with those of Dr. Salk.

Dr. H. A. Wenner, Kansas City, Kan.: We are one of the members of a team who are engaged in the program of typing poliomyelitis viruses by that extremely cumbersome method using monkeys. I have just one question to ask Dr. Robbins. Much of the information is in relative terms, but in a typing program (over 100 strains now) the bulk of the strains are Brunhilde type, about 85%, and about 12% have been Lansing type and 2% Leon type.

Of the Leon type, I do not know the source of one strain. One strain has been reported, coming from the West Coast. I am interested to know, since the Boston group has such a large number of Leon strains in their typing by the tissue culture method, whether the strains came from a focal outbreak in Boston or rather represent a diffuse scattering of strains from a wide area.

Dr. F. C. Robbins, Boston: All the Leon strains were isolated from patients in the summer of 1950; the majority of the patients came from the vicinity of Boston, although as far away as Deerfield, Mass.

The strains were obtained from patients with bulbar, typical paralytic, and nonparalytic disease, and also from the spinal cord of one patient who died.

DR. AIMS C. MCGUINNESS, Philadelphia: I should like to ask Dr. Adams if possibly there is any relationship between the site of injection of the gamma globulin and development of paralysis in those monkeys.

DR. ROBERT LAWSON, Winston-Salem, N. C.: We have been interested in the finding of Coxsackie virus during the 1948 epidemic in North Carolina. As some of you may know from reading the work of the Yale group, sera from about 300 normal Winston-Salem children were tested. There was an increase in antibody to the Coxsackie virus in about 50% of that group of apparently well children during the summer of 1948. However, it was somewhat surprising to us that when we checked the stools of about 70 patients admitted with "poliomyelitis," we found Coxsackie virus in only four of the specimens.

It brings up the fact that the role of Coxsackie virus in clinical "poliomyelitis" is still confused. Here, the Coxsackie virus was present in the community at the same time that the poliomyelitis virus was present. The problem remains of its role, both in imitating poliomyelitis and in the possibility of its changing the course of poliomyelitis infections. One cannot say that Coxsackie virus alone caused the disease which resembled poliomyelitis in our patients, including the one paralytic patient, but monkeys inoculated with stool extracts from these same four patients did not show the lesions of poliomyelitis.

DR. ROBERT WARD, New York: I think it is striking that almost simultaneously, after a long period of drought, two glassware tests for the recognition of poliomyelitis have been developed; the one reported by Dr. Robbins you have heard. The second one concerns a complement-fixation test which has been developed by Dr. Casals and Dr. Olitsky at the Rockefeller Institute. The trick there was to adapt a Lansing type of poliomyelitis virus to newborn mice, and the complement-fixing antigen was prepared from the central nervous system of the newborn mice.

We have available now, therefore, probably two practical glassware tests by which poliomyelitis infection can be detected. It is highly probable that the answers to a great many epidemiological questions, such as the one that I believe Dr. Adams raised concerning how many nonparalytic cases we have in proportion to the number of paralytic cases, can now be found.

I should like to ask Dr. Robbins, in an attempt to make a crossover, perhaps, between these two extremely important developments, whether or not he and his colleagues have tried to make a complement-fixing antigen from their tissue culture materials.

DR. ALEX J. STEIGMAN, Louisville: Dr. Robbins' findings have certainly opened up new avenues. The very thought of taking virus from human feces and growing it in human tissue culture without animal passage, as in the case of uterine tissue cultures, will make possible new approaches from the standpoint of immunization which were once considered closed.

I should like to ask Dr. Curnen if he would comment a little bit on the subject of the demonstration of poliomyelitis virus in some of these fecal samples. There is extant the impression that nonparalytic poliomyelitis occurring during local outbreaks of paralytic disease may represent purely a Coxsackie virus infection in the nonparalytic patients. It will be recalled that isolation of poliomyelitis virus is sometimes made only with the greatest of difficulty. Thus, in the Ohio strains to which Dr. Curnen referred the demonstration of poliomyelitis virus was possible only by detailed histologic study of olfactory bulbs of monkeys. It was, in our laboratory, extremely difficult to say that it was poliomyelitis virus, except for the histologic study. This was at a time that the Coxsackie virus had not yet been isolated. To this should be added the fact that Dr. Dalldorf, in describing the first two patients with paralytic illness from whom Coxsackie virus was isolated, indicated that poliomyelitis virus was apparently absent from their stools, which had been inoculated intracerebrally into rhesus monkeys. He subsequently found the poliomyelitis virus in the stools by feeding the same specimens to cynomolgus monkeys. This is mentioned only as an indication of how difficult it is to say that the stools are free of poliomyelitis virus. I wonder if Dr. Curnen would care to comment on this.

DR. J. M. ADAMS, Los Angeles: Dr. McGuinness asked whether there was any correlation between the site of inoculation of the gamma globulin and the paralysis. I think we can answer that in the negative. Most of the gamma globulin was given in the thickest muscle in the lower extremity. You recall we were giving very large amounts. Most of the paralysis we noted was in the upper extremities.

I should like just to mention an unpublished paper by Dr. Gaylord Anderson in which he has shown that immunization following diphtheria-tetanus-toxoid vaccination has shown a higher incidence in the arm inoculated or vaccinated and that there is no correlation with other types of inoculations, such as penicillin or saline.

DR. E. C. CURNEN, New Haven, Conn.: In regard to Dr. Steigman's question, it might be worth emphasizing the well-known facts that poliomyelitis virus can induce in man and animals either paralytic or nonparalytic disease and that, as Dr. Adams mentioned, we lack precise knowledge on the ratio of paralytic to nonparalytic illnesses caused by poliomyelitis viruses.

Evidence has been obtained that Coxsackie viruses can cause human disease without paralysis. This is indicated by the results of epidemiological studies and from observations on laboratory workers who contracted infection with these agents while working with them. It has not been shown, however, that Coxsackie viruses can cause paralytic disease in man. It remains for such evidence to be brought forward before we can conclude that Coxsackie viruses are capable of inducing the type of paralysis which we now attribute to infection by poliomyelitis virus.

DR. F. C. ROBBINS, Boston: Dr. Ward asked whether we had tried using the tissue culture materials as antigens in complement-fixation tests. We have not done a great deal, Dr. Ward. Obviously, it is something that we hope might be made possible by the tissue culture method, but the few preliminary runs that we have done so far have not given us any positive results.

Aureomycin Treatment of Streptococcal Disease: Prevention of Rheumatic Fever.

CAPTAIN GEORGE C. ECKHARDT, M.C., U.S.A.R. (by invitation), CAPTAIN HAROLD B. HOUSER, M.C., U.S.A.R. (by invitation), CAPTAIN EDWARD O. HAHN, M.C., U.S.A.R. (by invitation), MAJOR FLOYD W. DENNY, M.C., U.S.A.R. (by invitation), CAPTAIN DANIEL STOWENS, M.C., U.S.A.R. (by invitation), CAPTAIN LEWIS W. WANNAMAKER, M.C., U.S.A.R. (by invitation), Warren Air Base, Wyo., and DR. CHARLES H. RAMMELKAMP JR. (by invitation), Cleveland.

Previous studies have established that treatment of acute streptococcal infections with penicillin reduces the incidence of rheumatic fever. A similar study was conducted to assess the effect of an orally administered antibiotic, aureomycin, on the subsequent occurrence of rheumatic fever.

A total of 1,951 patients with exudative tonsillitis or pharyngitis were studied and divided into treated and control groups according to the United States Air Force serial number. Aureomycin was administered to 966 patients with even serial numbers in doses of 8.5 to 11 gm. over a four-day to six-day period according to one of three dosage schedules. There were 985 patients with odd serial numbers who received no therapy and served as controls.

Definite rheumatic fever occurred in 22 patients from the control group within 31 days after the onset of a streptococcal infection, whereas only three cases of rheumatic fever occurred in the treated group during this period.

Aureomycin therapy also caused a reduction in the convalescent carrier rate for group A streptococci and inhibited the formation of antistreptolysin. The dosage schedule of 11 gm. given for six days was the most effective in inhibition of antistreptolysin.

These studies demonstrate that aureomycin therapy of acute streptococcal respiratory infections is effective in the prevention of rheumatic fever.

Because the attack rate of acute rheumatic fever is related, in part, to the magnitude of antibody response to streptococcal infection, it is recommended that one employ that dosage schedule of aureomycin which results in maximal antibody inhibition. Therefore, treatment of streptococcal infections with aureomycin should be continued for a minimum of six days.

DISCUSSION

DR. JOHN DINGLE (by invitation), Cleveland: Dr. Ward has asked me to make a few comments on this paper. I am very happy to do so because I am extremely interested in the work this paper presents and the work that has gone on beforehand at Warren Air Base.

It has been clearly demonstrated, for the first time, I believe, that it is possible to prevent rheumatic fever. All rheumatic fever obviously cannot be prevented, since all patients are not seen during the preceding streptococcal infection. But the work that has been done previously

on penicillin and the work on aureomycin that is presented here today by Captain Eckhardt has been carefully carried out under strictly controlled conditions—the sort of conditions which are almost impossible to obtain in civilian life.

There is another point about the significance of the results that is of considerable interest and that Captain Eckhardt did not mention. This is that the observers following these patients did not know which patients had been treated with one or the other drug and which patients had not been treated. The results of these studies indicate very definitely that the frequency of occurrence of nonsuppurative complications can be markedly reduced by either antibiotic agent.

There are certain questions that should be raised and perhaps might be discussed in relation to this paper. Penicillin and aureomycin are apparently effective in treating streptococcal infections and in preventing rheumatic fever. Which drug is the preferable one? I think it should be emphasized that streptococcal infections, as you know, are self-limited and are usually over in three to five days. This raises a practical problem in the administration of the drug, particularly in persuading the patients to take it. I should like to ask Captain Eckhardt if he would elaborate on these problems.

CAPTAIN GEORGE C. ECKHARDT, M.C., U.S.A.R. (by invitation): Thank you, Dr. Dingle. In answer to the question of which drug, penicillin or aureomycin, would be preferable as the agent with which streptococcal infection should be treated, we can say this: In a similar study in which repository penicillin was used, the results were in some ways similar to those presented in this study of aureomycin. Penicillin and aureomycin are similarly effective in the prevention of rheumatic fever and are similar in their action in terms of the number of significant antistreptolysin increases which are inhibited by these drugs. However, penicillin is a more efficacious agent in termination of the carrier state. This difference might be most applicable to a military population.

A point for consideration is that some patients are prone to discontinue drug therapy prematurely because their symptoms have disappeared. In these instances, treatment of streptococcal infection with parenteral penicillin would be preferable to insufficient treatment with aureomycin. To reiterate, if aureomycin is the drug to be used, it should be given for a minimum of six days.

New Phenomenon: Production of Recurrent Parasitemia in Chronic Toxoplasmosis by the Injection of Potent Specific Antisera and Its Inhibition by Corticotropin (ACTH) and Cortisone. DR. HEINZ EICHENWALD (by invitation), New York.

The obligate intracellular protozoon parasite Toxoplasma is able to infect most animals and birds and to cause a disease in human beings. A latent, subclinical infection is known to occur in man and has been produced experimentally in mice by Weinman. The lesions in these chronic carrier mice consist of "pseudocysts" containing many viable organisms but characteristically evoking little or no cellular inflammatory response in the host's tissues.

In a series of experiments mice chronically infected with Toxoplasma and with no demonstrable parasitemia were inoculated intraperitonally with single doses of anti-Toxoplasma sera of very high neutralizing titer, produced by repeated injections of viable Toxoplasma into donor animals. Within two to four hours or less a parasitemia could be demonstrated in the chronic carriers, along with a recurrence of inflammatory lesions. Both quickly subsided. This phenomenon could be produced with high-titer anti-Toxoplasma sera from mice, guinea pigs, and rabbits; less potent antisera from humans and mice failed to evoke such an effect. Anti-pneumococcus serum, tetanus antitoxin, refined human "immune serum globulin," and normal sera failed to provoke a parasitemia.

Pepsin digestion and warming the sera to 68 C. destroyed both the neutralizing antibody component and the ability to produce a parasitemia. Corticotropin (ACTH) and cortisone injected two hours and one hour, respectively, prior to the antiserum injection inhibited its effect. Antihistaminics were ineffectual.

No material with antigenic properties could be demonstrated in the test sera, nor did known antigen produce a parasitemia when injected into the chronic carriers. The factor responsible for the occurrence of the exacerbation was not further identified but is thought to be associated with or be a part of the antibody component.

DISCUSSION

DR. HARRY FELDMAN, Syracuse, N. Y.: I think it should be pointed out that there are marked differences in our experiences from those of Dr. Eichenwald. These are due, I think, to the differences, perhaps, in strains reported, and with the RH strain of Toxoplasma, which was isolated by Dr. Sabin several years ago, we have been able to demonstrate a single parasite which inevitably causes fatal infection in mice. We have never seen a single mouse survive infection with one parasite. The same has been true with the B-17 strain, which we isolated in Cincinnati, a few years ago in a pigeon; consequently, we have never had a chance to study a mouse which had survived infection.

We have always explained that on this basis: Some of you may recall a paper which Dr. Sabin and I presented in which the dye test was stated as showing an accessory labile factor present in most human serum and most other animal serum necessary for the action of the antibody. The mouse is rather unique in that it does not have this factor and also does not have complementary activity, and we felt that the reason the mouse was so uniformly susceptible was that it did not have the accessory factor necessary to produce killing of the parasites.

We have never been able to show that the presence of an antibody which is a labile factor would ever kill parasites that kill cells. They remain immune. So we felt, on that basis, that we could explain the reasons why or the phenomenon whereby the mice would die inevitably with an infection with a single parasite.

However, the two strains we used, as well as other strains, are quite different from Dr. Eichenwald's, and it may be that the one he used behaves differently, or there is something fundamentally different about it, with the result that the virulence and invasiveness are different from those of the other strains which have been isolated to date.

I should like to point out to you, as an aside, that we have had within recent weeks an opportunity to study two fatal infections with Toxoplasma in adults. These are the first two I know of to have been proved for the last perhaps eight or nine years. One of them occurred in a 60-year-old woman in Boston. Fortunately, we were able to have serial samples which showed that there was no demonstrable antibody early in the disease, but she died three months later despite a rise in antibody titer. We could not get titers as high as Dr. Eichenwald mentioned he can obtain with the disease.

This woman, at death, had innumerable pseudocysts from Toxoplasma in all the tissues. Every muscle in her body had innumerable pseudocysts, in spite of intensive therapy with aureomycin, penicillin, chloramphenicol (chloromycetin®), and corticotropin, and a few other therapeutic measures that were used.

The second patient was seen about two weeks ago, and it was the first infection I know of to have been contracted in the laboratory—a fatal infection. The technician lived nine days after the first manifestations of the disease, and here again we obtained serial samples that were negative to begin with, with a progressive rise in titer, and by the day of death she had a titer of 1:256.

These are two of the most interesting instances I ever had an opportunity to study, because in each instance there was a demonstrable antibody and a change in antibody titer, and despite the presence of antibodies both patients later died.

Incidentally, in neither instance was the pathologist able to explain from the gross autopsy findings why the patient died. There were pseudocysts present in both persons, which, I believe, supports again previous findings of pseudocysts; the organism within the cyst at least seems to be safe from the action of the antibody. These patients had adequate amounts of the labile accessory factor, and death did not occur because of that.

I should also like to mention here, if it is not out of order, that many of you have received a questionnaire from me, or you will find it on your desk when you return home, regarding certain cases we have studied for you. We have about 45 instances of a general disease found within the past year. I will appreciate your filling out this questionnaire in order that we can organize the data and be able to give you conclusions on the basis of a broad experience rather than on certain isolated cases.

DR. R. A. GOOD, Minneapolis: I was extremely interested in this study of activation of latent infection. Some years ago we rather fortuitously ran across a method by which we could activate latent herpes simplex virus infection in rabbits, and it was of interest that one of the best

methods for activating that infection was to give animals anaphylactic shock against unrelated foreign protein. I wanted to ask the author whether or not this control had been done in his material.

DR. HEINZ EICHENWALD (by invitation), New York: I want to thank Dr. Feldman for his comments.

The tremendous difference between Toxoplasma strains has given considerable difference in results. Chronic toxoplasmosis was first described in 1941 by Dr. Weinman, and he had at that time in his possession two strains, none of which would kill mice unless injected intracerebrally, but in all cases the infection would go on to the chronic state with eventual death of the mice. That I demonstrated to you.

The RH strain even differs depending on the laboratory in which it is maintained. I think there may have been a possibility in the continuous animal passage, which is necessary, particularly if the strain is passed through guinea pigs and rabbits, that other strains have been picked up. The strain we used here is a different strain from those generally used in the literature, the RH strain being the favorite one. We use it simply because it is more convenient for us to use this one. It is less fatal, and we can maintain it in mice without having to passage it more than once a week.

There is another strain at Columbia, I believe, which produces essentially the same effect; there is the strain Dr. Isabel Grace isolated from a patient with toxoplasmosis which uniformly failed to kill mice but which would produce a chronic state. However, this particular strain would kill guinea pigs.

In answer to the second question, I have tried, before this study was attempted, to cause flare-ups of chronic toxoplasmosis by a large variety of means, including hemorrhages, pregnancy, and anaphylactic shock. The mouse is not a very suitable animal for anaphylactic shock experiments, as you know. In our experiments, if the antibody titer was eliminated, the exacerbation did not take place, which seems to point to the fact that the antibody component or something related to it is the responsible factor, and it is not something inherent in the foreign protein injection.

In rabbits, in which the chronic disease can be produced with some difficulty, injections of horse serum at various intervals, producing very severe anaphylactic shock, will not cause an exacerbation.

Intranuclear Inclusion Bodies in Tissue Cultures Inoculated with Varicella Vesicle Fluid. DR. THOMAS H. WELLER (by invitation) and M. B. STODDARD, B.S. (by invitation), Boston.

Attempts to isolate a specific agent from specimens of vesicle fluid and throat washings collected during the acute phase of chicken pox are described. Serial passage of these materials in the embryonated hen's egg failed to yield an agent. However, with use of a human embryonic suspended-cell tissue culture system, inoculation of vesicle fluid material was followed in five consecutive experiments by the development of eosinophilic intranuclear inclusion bodies. In these experiments a modified Maitland culture technique was employed. Minced tissue was added to flasks containing 3 cc. of nutrient medium. The inocula, added in 0.1-cc. amounts, consisted of vesicle fluid material which had been collected in sterile skim milk and stored in ampules in the solid carbon dioxide cabinet. By changing the supernatant nutrient fluid at three-day to five-day intervals, the cultures were maintained for periods ranging from 10 to 17 days. In all experiments control sets of cultures, either uninoculated or else inoculated with sterile skim milk, were maintained in parallel with the inoculated cultures. At various intervals fragments of tissue from the cultures were fixed in Zenker's solution without acetic acid and stained with hematoxylin and eosin.

In the five experiments in which inclusion bodies were demonstrable, the tissue substrate consisted of material from embryos of two to three months' gestation. Four different lots of tissue and three different vesicle fluid inocula were employed in these experiments.

Eosinophilic intranuclear inclusion bodies were observed as early as five days and as late as 15 days after inoculation. Characteristically the affected nuclei showed disruption of the normal nuclear structure with concentration of the basophilic chromatin along the nuclear membrane and with the inclusion occupying a clear, centrally located area. The inclusions

were homogeneous in structure and varied in size, at times filling the nucleus. They were found in several types of tissue, including epithelium, nervous tissue, and endothelial and connective cells. No intranuclear inclusions were observed in material from control cultures. These observations suggest, but do not prove, that the inclusion bodies were induced by the action of the varicella virus.

DISCUSSION

DR. ALFRED L. FLORMAN, New York: I should like to ask Dr. Weller whether herpes zoster has been used as an inoculum in any of these cultures and, secondly, whether an opportunity has yet arisen to examine this material under the electron microscope.

DR. MARGARET H. D. SMITH, New Orleans: I should like to compliment Dr. Weller on a very beautiful paper and another very pretty application of the tissue culture method to the study of viruses. I believe Dr. Weller said that the varicella virus had not previously been demonstrated, but I think that Dr. Rake and Dr. Scott presented before this society two or three years ago some photographs of varicella virus beautifully demonstrated by means of electron microscopy.

DR. GEOFFREY RAKE, New Brunswick, N. J.: I want to congratulate the group on this extremely fine study which I think should add to the work on this virus, or perhaps groups of viruses, which up to the present time has proved so hard to attack.

One point that I did note on the first slide shown was that no matter what it was that they had obtained so far which produces these results in tissue culture, they apparently get it with vesicle fluid taken two, three, and four days after the lesion was first seen. That, to me, is somewhat surprising, because, at least from the studies we have done, the virus does seem to leave the lesion very quickly.

When one makes up suspensions to try to see the virus, using the technique that Dr. Smith has just talked about, or when one carries out agglutination studies with fluid from the lesion and convalescent sera, it is extremely hard to find any virus in the fluid from the lesions except in those samples obtained during the first 12 to 16 hours following the time that that particular lesion was first seen.

DR. THOMAS H. WELLER (by invitation), Boston: With regard to Dr. Florman's question about herpes zoster, we have tried just one experiment, in which the material wasn't too satisfactory, and no inclusion bodies were seen. We have done no electron microscopic studies whatsoever.

In regard to Dr. Smith's comment, I, of course, meant to imply that the varicella virus had not been isolated and propagated, not that it has not been pictured with the electron microscope, as Dr. Rake and his group have done.

With regard to Dr. Rake's remarks about the rapid disappearance of elementary bodies from the maturing lesions, perhaps my comments have been somewhat misleading. The days indicated on the slide were days after onset of the first symptoms, such as malaise and headache. We collected vesicle fluid from fresh lesions as they developed in successive crops, and the vesicle fluids employed in these experiments were collected when the individual lesions were a few hours old.

I should like to add that Dr. Lawrence C. Kingsland Jr., working at the Children's Hospital, Boston, and using a somewhat different tissue culture system, also has been able to obtain intranuclear inclusion bodies after inoculation with varicella vesicle fluid. His call back to active service in the Navy has interrupted his studies along this line.

Second Session

Wednesday Afternoon, May 2

Middlebrook-Dubos Hemagglutination Reaction: A Study of the Test in Children.
DR. H. W. ANDERSON (by invitation) and DR. R. V. PLATOU, with the technical assistance of SUE SPATAFORA, M.S. (by invitation), New Orleans.

The Middlebrook-Dubos reaction involves the hemagglutination of tuberculin-sensitized sheep erythrocytes by sera from patients or animals with active tuberculosis. Other reports have indicated that it has a considerable usefulness in studies of tuberculosis in adults, that reactions

are usually positive with active tuberculous disease and negative in healed or terminal cases, that there may be a "provocative" rise in titer after cutaneous tuberculin testing, and that there are usually positive reactions with sera from patients with leprosy but with no other disease studied to date.

Reasoning that this test might be useful to pediatricians, frequently confronted with the problem of determining how a child with a positive Mantoux reaction is handling his tuberculosis, the present studies were initiated.

At irregular intervals 343 sera were taken from 287 sick or well infants and children in our pediatric wards, outpatient departments, and tuberculosis clinics. Later, results of these serologic tests were set up against all other available pertinent evidence of tuberculous or unrelated disease. Patients and sera were considered subsequently in four groups: group A, negative Mantoux reactions and no other evidence of tuberculosis (184); group B, apparently benign primary infections (45); group C, questionably active or healing tuberculosis (62); group D, definitely active tuberculosis (52).

No correlations were apparent as to sex, race, or effects of nontuberculous disease. Results of all tests, expressed as percentages having noteworthy titers, appear in the tabulation.

	Patient Group			
	A	B	C	D
Mantoux reaction	−	+	+	+
Clinical diagnosis	−	−	?	+
Serologic reactions				
Negative or positive in 1:2 dilution, %	93.5	68.9	54.8	53.8
Positive in 1:4 dilution, %	4.3	11.0	16.1	9.6
Positive in 1:8 dilution, %	0.5	17.7	16.1	15.4
Positive in 1:16 dilution, %	1.1	2.3	9.6	13.4
Positive in 1:32 dilution, %	0.5	...	1.6	1.9
Positive in 1:64 dilution, %	...	...	1.6	5.8
Total positive in 1:4 dilution or more, %	6.5	31.1	45.1	46.2

Apparent discrepancies relating to lack of selectivity (7% of children with negative Mantoux reactions having hemagglutinins) and specificity (many children with positive skin reactions but negative or negligible serologic reactions) were found to be generally explainable on three reasonably predictable bases:

First, a provocative effect of positive or negative skin reactions, producing an irregular and transient increase in hemagglutinins; this effect is dissipated within a month or two after skin testing.

Second, state of disease; hemagglutinins were absent in sera from infants with obviously terminal tuberculosis and absent or only transiently present in sera from children judged to have apparently benign primary infections.

Third, an age factor; hemagglutinins were not found in sera from any infants less than a year old, but they were present in sera from all children 6 or more years of age with active tuberculous disease. Sera from more than half of the questionably or definitely tuberculous patients between 1 and 6 years of age lacked noteworthy titers. This age factor apparently makes "unexpectedly" negative hemagglutination reactions quite meaningless in most infants and small children.

At this stage of our work, pending further experience to include longer follow-up studies and more adequate serial titrations during therapy of more patients with active tuberculous disease, we feel that the Middlebrook-Dubos test will probably be a useful additional procedure for studying tuberculous processes in infants and children.

DISCUSSION

DR. E. F. RABE, Kansas City, Kan.: We have had occasion to conduct a similar experiment at the University of Kansas. Inasmuch as there are a number of dissenting opinions concerning the value of this test, and inasmuch as there apparently are different "normal" values used, I thought it might be appropriate to say very briefly something concerning our own results.

We studied 110 patients who were tested with tuberculin; 30 of these had active tuberculous disease. We standardized our serologic levels on the basis of clinical activity in comparison with the level of the serum hemagglutinins. As a result, we found that all the patients who had no evidence of tuberculosis had hemagglutination titers of 1:32 or lower, with 4% having titers of 1:32; whereas 87% of the patients with evidence of active disease had titers of 1:32 or higher. Therefore, there was a 13% incidence of insignificantly elevated serum hemagglutinins in patients with active disease. All the patients with low titers were severely ill.

We were unable to find a relation between age and antibody response, but our patients were not under 4 years of age.

A final thing that was of interest was this—and I wonder if the New Orleans group has any comment on it: We had six patients with tuberculous meningitis, three of whom had obvious clinical evidence of tuberculosis in other parts of the body, namely, cervical adenitis or pulmonary lesions. Three of them had no clinically demonstrable extrameningeal tuberculosis. Serial serum studies were made of all of these. Regardless of age, those patients who had no evidence of extrameningeal tuberculosis had what we considered to be "normal" serum hemagglutinin levels, whereas those patients who had tuberculous meningitis and extrameningeal tuberculosis had significantly high levels, these being the highest we recorded, i. e., 1:256.

Dr. Aims C. McGuinness, Philadelphia: I should like to ask if BCG vaccination results in the elevation of these antibodies.

Dr. H. W. Anderson (by invitation), New Orleans: In answer to the first question, we were unable to find a correlation between height of titer and type of tuberculous infection. A number of our patients did have tuberculous meningitis, and in some of these we found the highest titers.

As to BCG vaccination, Smith and Scott have shown that antibodies as demonstrated by the Middlebrook-Dubos test do appear after the procedure, though they were not present beforehand.

Biochemical Target of Flexner Dysentery Somatic Antigen. Dr. F. W. Barnes Jr., Dr. H. Lupfer (by invitation), and Dr. S. Henry (by invitation), Baltimore.

When purified Bacillus dysenteriae (Flexner III, old name, Andrewes and Inman Z) somatic antigen, labeled with I^{131}, is injected into the vascular system of a rat, it is distributed within four hours to most body tissues. Given intraperitoneally, only 10% is absorbed over 18 hours.

The antigen is present in tissues at 18 hours in such concentration as to indicate its presence within the cells of all organs except the brain. The colon is notable for its low concentration and the liver for its extremely high one. Excretion occurs through the kidney and only slightly in the feces, there being a thirtyfold concentration of the antigen by the kidney. The concentration value for the blood is close to that of many of the organs, and the blood retains significant activity after 72 hours.

By 72 hours after injection much of the antigen has left the liver and several other organs and has been either excreted or taken up by muscle, sex organs, and a few other tissues.

It is concluded that this toxin-antigen after absorption passes freely through capillary and cellular membranes and circulates in body fluids in a dynamic and reversible equilibrium with a specific, cellular, biochemical target with which it interacts to produce in some way signs of toxicity in a manner of minutes after reaching the blood stream. The approximate $L.D._{\infty}$ concentration of antigen in rat blood appears to be about 40 γ per gram. The target is contained to varying extent or specificity in the cells of most tissues, the liver being by far the most important and the colon not a primary site at all. In the liver the target appears to be contained chiefly in the hepatic cells. The other components of the equilibrium are excretion through the kidneys and absorption from some depot or source. Degree of toxicity is a function of concentration of the antigen in body fluids, and the effect of toxin on the biochemical target is not appreciably cumulative.

After 18 hours there is evidence of a tissue reaction which lessens the effect of the toxin depot, and by 72 hours there is evidence of tissue response in some cells, such as muscle, leading to an increased capacity for combining with the antigen. A role for this and other targets in the production of immunity by means of a local regenerative response is postulated.

Experimental Hypersensitivity: A Study in the Relationship of Corticotropin (ACTH) and Adrenalectomy to the Serologic Sequence and Production of Pathological Lesions Following Injection of Heterologous Serum Protein. Dr. Frederic C. Moll (by invitation), Seattle, and Dr. Clinton Van Zandt Hawn (by invitation), Cooperstown, N. Y.

Previous studies have been reported which have shown that characteristic lesions can be produced regularly in the rabbit after a single large injection of purified heterologous serum protein. When bovine gamma globulin is used, the lesion most frequently seen is a glomerulitis characterized by increased size and number of capillary endothelial cells and an infiltration of glomerular tufts and mesangium by inflammatory cells, including polymorphonuclear leucocytes and monocytes. Occasionally there is exudate in the subcapsular space. These changes occur about 8 to 10 days after injection of the protein, and healing takes place promptly by resolution with the occurrence of circulating antibody. During this acute phase there is a transient depression of the level of circulating blood complement. The return to normal levels is associated with the appearance of circulating antibodies. The lesions seen are thought to be due to local antigen-antibody interaction with possible utilization of complement. Whether complement is necessary for the production of the lesions is problematical, but its sudden depression occurring at the time of appearance of the lesions may be an indication of antigen-antibody interaction. Other investigators have demonstrated that lesions due to experimental hypersensitivity may be prevented by the use of corticotropin (ACTH) and cortisone when antibody production is not entirely depressed. The purpose of experiments reported here was to determine whether adrenal stimulation or insufficiency might alter the serologic sequence and pathological findings.

The first chart shows the results in the normal animal. The blood complement in the uninoculated control group shows very little change. When animals are given one injection of 1.0 gm. per kilogram of body weight of bovine gamma globulin, all rabbits show a transient depression of the circulating blood complement about the 8th to 10th day. This depression of complement is followed by the appearance of circulating antibodies, and all of these animals autopsied at 14 days had demonstrable lesions. In an attempt to create a severer renal lesion, a second injection of globulin was given at 10 days after first desensitizing with a small dose on the ninth day. These animals showed the beginning of a second depression of the blood complement titer. Four of the animals had antibodies at nine days, and all were autopsied before antibodies could be demonstrated after the second injection. Three of these rabbits had lesions; the rest did not. It is of speculative interest to note that these were three of the four who had antibody formation at the ninth day.

In a similar group of animals given 20 mg. of corticotropin (Armour LA-1-A Standard ACTH) intramuscularly in four divided doses daily, the serologic sequence remained unchanged. The complement titer in the controls showed little variation. In those rabbits given a single injection of serum protein, the drop in complement occurred; all had antibodies, as demonstrated by the ring test, yet none had lesions at a time that lesions may be reasonably expected to be demonstrated. The twice inoculated animals showed the same two depressions of complement, and lesions were not demonstrable at the time of death. The only variation seen was a delay in the drop in circulating complement and appearance of antibody for one to two days on the average, but the gross changes were similar.

An experiment designed to demonstrate the effect of adrenal insufficiency was performed. Two-stage adrenalectomies were done, and the animals were given some supportive therapy with desoxycorticosterone (doca®) acetate and saline solution. All animals had signs of adrenal insufficiency confirmed by blood sodium levels, and half the animals died with typical signs of adrenal failure. In the singly inoculated animals the same complement pattern was seen, and in all antibodies developed. Unfortunately, owing to the autolysis following death and the time of autopsy in those animals which lived, the pathological studies are not comparable to the preceding experiments. However, of the two surviving animals, one had unequivocal residual lesions 24 days after the initial injection. In the twice inoculated animals the same serologic pattern can be seen. The double phase in complement is more obvious as the experiment was carried to 32 days. Again, however, the histologic studies were unsatisfactory because of death or prolonged survival.

Preliminary observations made on a small group of rabbits given 10 and 5 mg. of cortisone demonstrated no change in the circulating complement in the control group. In those given a single injection and then killed at 14 days, no change in complement was found; antibody did not develop, and no lesions attributable to antigen-antibody interaction were seen. However, this experiment is too limited to warrant further comment.

In summary, evidence has been presented that alteration of the circulating blood complement and the formation of antibodies in the rabbit following a large dose of heterologous serum protein are not altered by corticotropin or adrenalectomy. However, if the animals are given corticotropin, the lesions attributable to antigen-antibody interaction are prevented. This is in accord with published reports of the effect of corticotropin on antibody formation and development of lesions. Presuming that the complement titer is an index of antigen-antibody interaction, the experiments give additional support to the concept that the effect of adrenal stimulation is not on the antigen-antibody union but on the reaction of the host.

DISCUSSION

DR. CHARLES A. JANEWAY, Boston: I take a little fatherly pride in these experiments that have been carried out, since Dr. Moll started this work in our laboratory. He has carried it a long way further than we have, particularly this phase of it, and I think has clearly shown what Dr. Wedgwood in our laboratory showed, in a much more limited series of studies, that corticotropin merely alters the response of the animal to the noxious effects of the interaction of antibody with its antigen in the tissues.

The most provocative thing in his paper is the last chart. If the response to cortisone administration is quite different and does alter antibody production, then we may have to rethink a lot of our concepts. Dr. Eichenwald's paper this morning implied something a little bit similar, in that possibly we cannot compare corticotropin with cortisone simply because when we give the latter, an end product of adrenal stimulation, we are able to measure in milligrams the actual active principle that we put in, whereas when we stimulate with corticotropin we have no accurate way of knowing the extent of the production of hormones that have the same general type of effect as cortisone. I hope that he will go on with this series of experiments and try to quantitate them, since it may be that differences between the effects of corticotropin and cortisone are merely quantitative.

DR. FREDERIC C. MOLL (by invitation), Seattle: I purposely did not dwell on the last slide very long because the series is extremely small and, unfortunately, cortisone causes death in the animals rather regularly if there is an endemic diarrhea in the rabbit colony, which we had. The first experiment started with cortisone, in which a much larger dose was given, showed a great mortality and, actually, a marked depression of complement, so that it was no longer measurable. The smaller dose of 10 to 5 mg. showed marked hematological effect, and we were never able to demonstrate any antibody formation in these animals.

Serum Complement Titers in "Collagen Diseases" in Children. LIEUTENANT RALPH J. P. WEDGWOOD, M.C., U.S.A.R. (by invitation) and DR. CHARLES A. JANEWAY, Boston.

Three hundred quantitative serum complement titers were determined (by a modification of the 50%-hemolysis colorimetric technique of Mayer and associates) on 70 patients with various "collagen diseases." These determinations indicate a definite pattern during the initial or active phases of these diseases. Patients with disseminated lupus erythematosus, acute glomerulonephritis, and nephrosis routinely showed low complement titers. In patients with nonthrombopenic purpura, with or without arthralgia, melena, or hematuria, the titers were close to, though slightly higher than, the normal range. Patients with dermatomyositis and rheumatoid arthritis routinely showed elevated titers.

During the healing, recovery, or therapeutically induced remission phases of these diseases these abnormal titers tended to return toward normal levels.

The low titers may be due to in vivo complement fixation, such as we believe occurs in experimental hypersensitivity to foreign protein in the rabbit, in which a depression of serum complement can be demonstrated concomitantly with the appearance of acute lesions. The high titers do not necessarily exclude an immunological mechanism.

We hope that further experimentation will lead to clarification of these data.

DISCUSSION

DR. GLADYS J. FASHENA, Dallas, Texas: I can't help wondering why it is that the collagen disease which gives us the most trouble, namely, rheumatic fever, was omitted from the study.

DR. CHARLES A. JANEWAY, Boston: The main trouble was that the patients were across the street, and we had all we could handle where we were.

LIEUTENANT RALPH J. P. WEDGWOOD, M.C., U.S.A.R.: Dr. Fashena, we had very few complement titers on patients with rheumatic fever, and I would hesitate to comment on them, since they were not all obtained during the acute phase, and also it took a long time to transport some sera from the House of the Good Samaritan over to the Children's Hospital.

Placental Transmission of Mumps and Streptococcus MG Antibodies. DR. ALFRED L. FLORMAN, DR. BELA SCHICK, New York, and DR. HOWARD E. SCALETTAR (by invitation), Brooklyn.

Mumps may occur at any age, but it is extremely rare in the neonatal period. This has been said to be probably due to the placental transmission of mumps antibodies. As a result of the recent development of specific serologic tests, it is now possible to obtain quantitative data concerning the permeability of the placenta to these substances.

The present communication reports the results of testing maternal and cord blood for mumps complement-fixing and agglutination-inhibiting antibody content. With the complement-fixation test, 23 of 25 mothers (approximately 90%) had antibody titers of 1:4 or above. In 18 sets both sera had exactly the same titer, and in five sets there was a difference of only a single dilution. Thus, within the limits of technical error, at the time of birth, in 23 of 25 instances the antibody content in the placental blood was quantitatively that of the mother. With the agglutination-inhibition test, the results were similar but even more striking. Forty-seven sets of sera were tested. In 41 both specimens had identical titers. The remaining six varied only by a single dilution. Therefore, with the agglutination-inhibition test, again within the limits of technical error, there was complete agreement between maternal and placental antibody levels.

The transmission of these two mumps viral antibodies from mother to child without loss is similar to what Dr. Schick showed many years ago to be true for diphtheria toxin.

These results stand in contrast to what was found with 25 sets of sera when they were tested for the presence of streptococcus MG agglutinins. These have been found in low titer in the sera of a number of apparently normal persons. They were therefore selected for comparison with the mumps antibodies, since they too represent naturally acquired antibody, though to a bacterium rather than to a virus.

There were 20 mothers who had detectable streptococcus MG agglutinins. In 16 of these 20 sets of sera (approximately 80%) there was a fourfold or greater decrease in titer between maternal and cord blood.

It cannot actually be determined at the present time whether the mumps viral antibodies are smaller in size or in aggregation than the streptococcus antibodies. However if they were, it would be a possible explanation for the foregoing results. Differences in antibody size or aggregation would perhaps also offer an explanation for some of the greater passive resistance of newborn infants to different viral and bacterial infections.

DISCUSSION

DR. HORACE L. HODES, New York: I should like to give a brief addendum to Dr. Florman's paper, in this respect, that some years ago Dr. Ziegler, Miss Zepp, and I studied the Type I pneumococcus mouse-protecting antibody titer of mothers and infants. We found that unless the mother had 1,000 units per cubic centimeter of mouse-protecting antibody or more against Type I pneumococcus the infant's blood contained no such antibody. When the mother's titer exceeded this figure, antibody was found in the baby's blood; a ratio of roughly 1,000 to 1 in favor of the mother was observed. When mothers who had no demonstrable antibody against Type I pneumococci were vaccinated late in pregnancy, such antibody developed, and some of it was transmitted to the babies; in these instances the ratio for the mother's blood to the infant's was 1,000:1, similar to that which Dr. Florman described here for the bacteria he studied.

DR. E. C. CURNEN, New Haven, Conn.: The agglutination titers against streptococcus MG which Dr. Florman found in mothers' sera were all within a rather low range. It is difficult to

determine whether agglutination in such low titer is specific or not. It might be questioned, therefore, whether the findings are truly representative of streptococcus MG antibodies and whether comparable results would be obtained in studies on mothers with higher titers.

DR. CHARLES A. JANEWAY, Boston: There are two things that I think are worth pointing out. I am sure Dr. Florman has thought of them both. The first is that with relatively low titers, as is true for these agglutinins, it may be that the adjuvant effects of certain of the lipoproteins may make considerable difference in titer. The only really good, careful studies comparing the lipoprotein content of maternal and cord blood indicate that the great difference lies in the lipoproteins, particularly the beta lipoproteins, which are abnormally high in the blood of the pregnant woman. This is a physiological change of some type in the mother's blood. In the infant, on the other hand, by electrophoretic analysis, gamma globulin is relatively higher than in the mother's blood, but we don't know what all that gamma globulin is. I think it would have been nice if Dr. Florman had shown a higher titer in the infant than in the mother with that in mind, but the differences would be relatively slight.

There is another point of great importance; antibodies aren't all alike chemically. Many people have pointed that out, but there is a great deal of work now which shows that the typical gamma globulins to which the placenta is relatively permeable, in which one finds the virus antibodies and diphtheria and other antitoxins, have a molecular weight in the neighborhood of 150,000. This type of antibody in allergic patients crosses the placenta after immunization or hyposensitization, whichever you choose to call it, since the so-called blocking or neutralizing antibody appears to have a molecule of this size.

On the other hand, antibodies to carbohydrate complexes, as for example the O antigen of the typhoid bacillus, the skin-sensitizing antibodies, the Wassermann reagin, all of these have components of much larger molecular weight, and it is quite apparent that they do not traverse the placenta as readily. For example, allergic skin sensitivity is not transmitted to the infant, but the blocking type of antibody is, indicating the molecular differences between the two types of antibodies.

I think all work on placental transmission of antibodies in the future must attempt to correlate this new physical-chemical knowledge with our knowledge of neonatal immunity.

DR. ALFRED L. FLORMAN, New York: I want to thank Dr. Hodes for his remarks about the pneumococcus vaccination program. He was good enough to show me those figures, and I was very pleased to see how they differed from the results of vaccination of mothers with influenza vaccine and how they resembled our streptococcus MG results. Whether this is a reflection of the difference in size of the antibody or, as Dr. Janeway pointed out, the fact that we were working with a carbohydrate, I do not know, but it is a very intriguing bit of business to keep us busy for a long time.

So far as the comments that Dr. Curnen made are concerned, none of our mothers had just convalesced from atypical pneumonia, consequently we were unable to find any that had titers much above 1:16. We were also concerned about these low titers, and in an attempt to find another "naturally occurring" bacterial agglutinin, we investigated a small group for the presence of Proteus OX19 agglutinins. In this group, too, we had very few that had high titers.

Immunochemical Study of Serum Albumin in Patients with Nephrotic Syndrome.
DR. DAVID GITLIN (by invitation), Boston.

Previous studies of the serum and urinary albumins in patients with the nephrotic syndrome have given rise to conflicting interpretations, some workers concluding that the albumin of nephrotic serum is abnormal in its chemical properties, others that it is normal. Immunochemical characterization provides a very delicate method for detection of differences in the fine structure of proteins. Accordingly, this method has been applied to study of the albumins of nephrotic serum, ascitic fluid, edema fluid, and urine, in an effort to determine whether or not these proteins differ from those found in the blood of normal humans.

Sera from 11 children with the nephrotic syndrome have been studied immunochemically, employing rabbit and equine antisera prepared against crystallized human serum albumin derived from the pooled plasma of normal adults by the low-temperature ethanol-water fractionation method. Quantitative albumin-antialbumin precipitation curves were obtained, employing suitable

dilutions of the serum of the nephrotic patients, and these curves were compared with those obtained by precipitation of the same antiserum with crystallized normal serum albumin. The curves were studied through all zones of inhibition and precipitation to permit as complete characterization as possible. Complement had been removed from all sera by adsorption with the system using Type III pneumococcus polysaccharide and rabbit antiserum. Ascitic fluid from eight of these patients, urine from six patients, and edema fluid from two patients were studied in a similar manner.

In the albumin-rabbit-antialbumin system, albumins from the serum, ascitic fluid, edema fluid, and urine of the nephrotic patients were immunochemically indistinguishable from serum albumin obtained from normal adults. The urinary albumin appeared to be indistinguishable from crystallized normal serum albumin in the equine antiserum system as well. The curves obtained with nephrotic serum and ascitic fluid in the albumin-equine-antialbumin system were slightly different from those obtained with crystallized normal serum albumin. However, they were identical with curves obtained with normal adult serum that had been adjusted by ethanol fractionation to contain the same relatively small proportion of albumin as is present in nephrotic serum. According to this evidence, there does not appear to be any immunochemical abnormality of the circulating serum albumin or of the albumin found in the edema fluid, ascitic fluid, or urine of these patients.

It also follows that the immunochemical method employing rabbit antiserum can be used for quantitative estimation of the concentration of serum albumin in the body fluids of the nephrotic patient. The hypoalbuminemia of the nephrotic syndrome in children appears to be very definite. The average albumin level, as determined immunochemically in the serum of the nephrotic patients studied, was 0.3 gm. per 100 cc. with levels ranging from 0.09 to about 0.5 gm. per 100 cc.

These studies, when taken with the established inability of the nephrotic kidney to retain injected normal human serum albumin, point rather clearly to the kidney as the site of the primary pathological process in the nephrotic syndrome, rather than to some metabolic abnormality in the synthesis of serum proteins.

DISCUSSION

DR. HENRY D. LAUSON (by invitation), New York: I was very pleased to see these results, because several years ago, in the process of determining albumin clearances in nephrotic children, we used an antiserum prepared against the Fraction V material, which is not a crystalline antigen. At that time, serum albumin levels in our few cases were only slightly higher than those just reported by Dr. Gitlin, that is, about 0.35 to 0.5 gm. per 100 cc. I think his data clearly indicate that the Howe fractionation method is not very useful for research purposes in the presence of severe hypoalbuminemia.

DR. CHARLES A. JANEWAY, Boston: I believe most of us have felt that Dr. Gitlin's conclusion was true, but the body of evidence which has been built up gradually as methods have improved has tended to confirm this.

There was a period in which the theory was widely held that a metabolic defect was the primary cause of the disturbance. An alteration of cellular metabolism rather than something wrong with the renal apparatus had its day, and a great many people have brought forth evidence to indicate that there was something abnormal with the serum proteins in nephrosis.

It is obvious that the serum proteins are about as normal as in any disease we study, but the abnormalities are abnormalities of the serum proteins as a whole. These are a polyglot population of at least 70 different molecules so far as we know. The crucial question is whether the individual proteins are abnormal, or whether the abnormality is simply an alteration of their proportions to one another. I come from an area where the school of thought hews very closely to the line of the chemical anatomist, that the molecule that does the physiological job is an anatomic entity, and it does not keep putting on a new coat every couple of days. When you actually can get that molecule in a pure state, I think the picture can be clarified, as Dr. Lauson and Dr. Gitlin indicated.

The first step is the injection of large amounts of albumin derived from normal blood into nephrotic patients; it can be recovered almost quantitatively in their urine, thus demonstrating that the nephrotic kidney cannot retain normal albumin. Now we have the second step, the

demonstration (and I should emphasize this), by the most delicate chemical tool we possess today for the study of the serum proteins, that the particular serum protein which is most deficient in nephrotic patients, serum albumin, is the same in the urine, the ascitic fluid, and the blood as the protein of normal adults, which it has already been shown these patients cannot retain.

DR. DAVID GITLIN (by invitation), Boston: I should like to thank Dr. Lauson and Dr. Janeway for their comments.

The question has been asked whether or not any studies have been done on the change in concentration of albumin during diuresis. Yes, it has been done indirectly, and yet directly. Goettsch and Reeves presented the first quantitative paper on the immunochemical characterization of serum albumin, or of the serum proteins, in the nephrotic patient. Goettsch and Reeves studied them by the precipitin method, using rabbit antiserum against normal serum albumin, but they used as a standard the Howe fractionation method. Because the precipitation obtained with rabibt antiserum during edema was less than the amount of albumin they found with the Howe fractionation method, they believed that the precipitin test indicated that the albumin was immunochemically different from normal serum albumin. If we ignore for the moment the Howe fractionation results completely and study the authors' data, we find that they also obtained during the edematous phase of the nephrotic syndrome the same low levels of albumin as we are now finding with rabbit and horse antiserum. These authors followed the rise in concentration of albumin during diuresis and found that the albumin levels rose steadily to a point where the albumin concentration was usually still below normal but nevertheless relatively high. At that time, coincidentally, the Howe fractions and immunochemical determinations agreed more closely, and therefore they concluded that in the nonedematous state the nephrotic albumin was less abnormal.

On one of these slides, I said that there were three patients demonstrated and yet there were five symbols. Actually, three symbols represented the same patient for whom paracentesis had been performed and for whom the albumin, after the edema had subsided, steadily rose. We did not study this particular patient over any great length of time, but in a period of two days the albumin level had doubled.

Measurement of Extracellular Fluid Space in Infants. DR. PHILIP L. CALCAGNO (by invitation), DR. GEORGE S. HUSSON (by invitation), and DR. MITCHELL I. RUBIN, Buffalo.

Inulin has been effectively used to measure the extracellular fluid space in nonedematous adults, and to date it is considered the most reliable measure of this space. It has been emphasized that the total collection of injected inulin is necessary for valid interpretation, the usual procedure taking approximately 10 hours or longer for the determination.

In order to apply this method in the study of sick infants, it is apparent that a test which can be completed in a much shorter period had to be employed.

Inulin (extracellular fluid) spaces were measured in eight nonedematous infants, six newborn and two older. Calculating the space at the termination of the equilibration period by subtracting the amount of excreted inulin from the amount of inulin injected, it is apparent that reliable estimation of this space can be made within a period of two to three hours, thus making the test more applicable for clinical use in sick infants.

Sodium ferrocyanide, a substance of smaller molecular weight than inulin, was used simultaneously in four of these infants to measure the extracellular fluid space. A method for determining ferrocyanide at low plasma concentration was used. At this plasma level (4 to 8 mg. per 100 cc.) no evidence of renal toxicity was noted in the infants studied. Ferrocyanide reached equilibration within a shorter time than was found with inulin (45 minutes). The ratio of ferrocyanide space to inulin space ranged from 0.96 to 1.04.

Comparative data on inulin, sodium ferrocyanide, and creatinine clearances are presented and their significance discussed.

DISCUSSION

DR. HORACE L. HODES, New York: Dr. Katcher has been working on this problem with Dr. Levitt, who is one of the people who developed the inulin space measurement. I wonder if you would be kind enough to ask Dr. Katcher for his comments.

DR. AVRUM L. KATCHER (by invitation), New York: We measured the inulin space in seven normal infants 2 to 6 months of age with the standard technique of four-hour to six-hour steady equilibrating infusions followed by twelve-hour urinary collection. Our values in these infants ranged between 24 and 28%, with an average of 25.6%.

In one patient with acute infantile diarrhea the inulin space and the total body water (in vivo dilution of deuterium oxide) were measured on admission and serially thereafter during convalescence. Intracellular volume was calculated as the difference between total body water and inulin space. During the stage of dehydration both extracellular and intracellular volumes were reduced, 25% and 16% respectively below average normal value. After five days of conventional fluid therapy repeat studies revealed a marked increase in inulin space with a proportionately smaller increment in total body water. Accordingly, although the extracellular compartment was expanded to 38% of body weight (50% above normal values), the intracellular compartment revealed a further decrement. After 13 days of hospitalization the inulin space reverted to normal values despite little change in total body water. The data for this one patient indicate that although the extracellular dehydration was rapidly overcome by conventional therapy, the intracellular dehydration persisted and actually became slightly more marked during the early stage of therapy. Furthermore, the correction of the intracellular dehydration did not occur until long after the extracellular compartment had been replenished, namely, four to seven days after fluid therapy had been discontinued.

DR. JACK METCOFF, Boston: I think Dr. Calcagno and his associates are to be complimented on an excellent study. I wonder if he would care to comment, for those of us who are rather interested in body composition, on whether he feels that the inulin or ferrocyanide space measurement is actually a measurement of extracellular space. That seemed to be treated insufficiently in the presentation.

DR. HENRY L. BARNETT, New York: I should like to say, too, that I think the introduction of this new technique for very much needed physiological measurement is an important thing. I should like to ask a question concerning the toxicity of this material, which I am sure Dr. Calcagno has considered and has data on.

The one other point I should like to make is the question of whether substituting this type of space measurements for balance techniques provides the answer to the problem. I think it is particularly interesting to note in Dr. Katcher's data, given in his abstract, that during the time body water increased over a liter, 1,050 cc., as measured by the deuterium space, the total body weight increased only 0.3 kg. This is a discrepancy which makes one worry about the accuracy of the measurement of these spaces.

DR. NATHAN TALBOT, Boston: May I add my compliments to the authors and ask one more question concerning the rate of equilibration of ferrocyanide in extracellular water. If he mentioned that, I missed it.

DR. HORACE L. HODES, New York: I believe that I can outline briefly Dr. Marvin Levitt's opinion of the data just presented by Dr. Katcher. The figures which were given mean either one of two things: (1) that water came out of the intracellular space into the extracellular space or (2) inulin entered tissue spaces from which it is normally excluded. I think there is no way of deciding which it is, and I think that point must rest there. I do not believe that the discrepancy between the change in the total water and body weight are attributable to either of these factors. The likelier explanation probably depends on the rapid protein catabolism which occurs early in the disease and therefore alters body weight independently from changes in total body water.

DR. MITCHELL I. RUBIN, Buffalo: The obvious conclusion that must have occurred to everyone also occurred to us, to try these substances in patients with edema. We are not prepared to discuss the question of the use of these substances in measuring extracellular space in the presence of edema. However, we have had the opportunity of studying three edematous patients. I should like to describe the results in one patient, because I think the data on this patient will raise considerable concern in all of us as to the validity of plasma equilibrium values in determining body water distribution in the edematous patient.

The patient was a 40-year-old adult with lupus erythematosus having the nephrotic syndrome. The plasma level of both sodium ferrocyanide and inulin reached equilibration at two and

one-half hours, and yet edema fluid measured in the leg at the same time showed no inulin, and sodium ferrocyanide was 15% of the plasma level.

This patient was studied at another time, when the determinations were made eight and one-half hours after the injection of the sodium ferrocyanide and inulin; plasma equilibration was present at eight and one-half hours (this was with continuous infusion), but the fluid obtained in the leg showed the inulin to be 19% of the plasma level and the sodium ferrocyanide 38% of the plasma level. We are not in any way happy about the possibility of using these substances for the measurement of "extracellular" fluid space in the presence of edema.

DR. PHILIP L. CALCAGNO (by invitation), Buffalo: I should like to thank Dr. Katcher for his comment.

Concerning Dr. Metcoff's question, of whether or not sodium ferrocyanide and inulin fluid spaces are truly a measurement of the extracellular spaces, I agree it would be better to designate them as ferrocyanide and inulin spaces.

In answer to Dr. Barnett's question as to toxicity, we have not found any evidence of renal damage when sodium ferrocyanide was used in the prescribed dosage. We have repeatedly examined the urines of these patients and in addition have done clearance studies on these patients, and we have not found any obvious disturbances.

Concerning Dr. Barnett's second question of whether or not the extracellular fluid determination could be a substitute for balance data, I should think the extracellular space measurement could be used in conjunction with balance data estimations.

In regard to Dr. Talbot's question (I don't know whether I understood the entire question), my understanding is that he would like to know the rate of diffusion of sodium ferrocyanide. Constant plasma values for sodium ferrocyanide, in terms of vascular equilibrium, occur within 30 to 45 minutes. I know of no determinations done on tissue fluids in normal persons relating the concentration of this substance to the vascular compartment.

DR. MITCHELL I. RUBIN, Buffalo: Just one other point regarding the toxicity of the sodium ferrocyanide. Sodium ferrocyanide was used in amounts to produce low plasma levels. This was made possible through development of a chemical technique devised by Dr. Husson for estimation of sodium ferrocyanide at low plasma concentration.

Effects of Sympathetic Nerve Division on the Renal Tubular Absorption of Electrolytes. DR. S. A. KAPLAN (by invitation), and DR. S. J. FOMON (by invitation), Cincinnati.

In a series of experiments on hydropenic dogs the greater splanchnic nerve, which contains most of the sympathetic fibers to the kidney, was divided on one side. By separate cannulization of the ureters specimens of urine were collected from each kidney. Osmotic diuresis was induced by the intravenous injection of hypertonic sodium chloride or hypertonic mannitol solution. The dose of injected sodium chloride was 2.5 cc. of 10% solution per kilogram. A maintenance infusion of 1% of this priming amount was infused every minute by means of a constant-infusion machine. Mannitol was injected in amounts calculated to achieve a concentration of 20 milliosmoles per liter in the plasma, and 1.5% of this injected amount was infused intravenously every minute until the end of the experiment.

The losses of sodium and chloride were always greater on the splanchnicotomized side. In one of the sodium-chloride-loading experiments, 45 minutes after nerve division the splanchnicotomized side excreted 906 μEq. (microequivalents) of chloride a minute, whereas the intact side excreted 130 μEq. a minute. Immediately before nerve division the splanchnicotomized and intact kidneys excreted 393 and 389 μEq. of chloride a minute respectively. The losses of sodium closely paralleled the losses of chloride in all of these experiments.

In an attempt to localize the site of action of the autonomic nervous system in the renal handling of electrolytes, a series of experiments was carried out in which glomerular filtration rates and electrolyte losses were measured simultaneously. In this series a few weeks were allowed to elapse between nerve division and the loading procedure, so as to minimize the vascular adjustments immediately following nerve division.

After injection of hypertonic sodium chloride into these animals, there was once again a greater loss of sodium and chloride from the splanchnicotomized than from the intact side. After a second injection of hypertonic sodium chloride this difference in electrolyte loss was

accentuated. In a typical experiment, immediately after the second injection the splanchnicotomized side excreted 3,088 μEq. of chloride a minute, as compared with 1,854 μEq. for the intact side. Twenty minutes later the splanchnicotomized side excreted 2,159 μEq. a minute, whereas the intact side excreted 798 μEq. a minute. The glomerular filtration rates as measured by exogenous creatinine clearance were nearly equal on the two sides throughout the entire experiment. For example, during the periods for which the chloride losses are given above, the creatinine clearances on the denervated and intact sides were 124 and 126 cc. a minute and 120 and 119 cc. a minute, respectively. The plasma chloride concentrations during these two periods were 132.8 mEq. per liter and 141.2 mEq. per liter respectively.

The greater excretion of sodium and chloride on the denervated than on the intact side in the presence of equal glomerular filtration rates has led to the conclusion that the sympathetic nervous system exerts some control on the renal excretion of electrolytes by a direct effect on the renal tubule.

DISCUSSION

Dr. Henry D. Lauson (by invitation), New York: I have several questions and a few comments I should like to make on this very interesting piece of work. First of all, have these studies been done without salt loading? Second, have mock operations been performed? Third, were measurements of glomerular filtration made during a control period before denervation, to see whether there might not have been a spontaneous difference of clearance on the two sides initially?

Dr. Mitchell I. Rubin, Buffalo: Was there a diuresis of water as well as sodium chloride on the denervated side?

Dr. Henry L. Barnett, New York: Certainly this question of the effect of nervous control on tubular function is an extremely important one, and evidence supporting it must be examined very critically. I should like to ask, for instance whether glomerular filtration rate was measured in the chronic experiments before splanchnicotomy to see if there was any difference between the two sides. Also, I should like to ask if renal plasma flow was measured in the acute experiments.

Dr. Cooke, New Haven, Conn: I should like to ask the authors if they measured the venous pressure on each side, in view of Blake's work on the difference in reabsorption with changes in pressure.

Dr. S. A. Kaplan (by invitation), Cincinnati: If I may take the questions in reverse order, first, we did not measure venous pressures.

In reply to Dr. Barnett's questions, renal plasma flow and glomerular filtration rate in acute experiments tend to differ more than they do in the chronic experiments. The slide which we demonstrated was from a chronic experiment. The control glomerular filtration rates on the two sides in these animals were almost equal.

In reply to Dr. Rubin, these were experiments conducted under conditions of osmotic diuresis in dehydration. Neither side, therefore, showed water diuresis.

In reply to Dr. Lauson, we have performed mock operations which do not yield these results. We have not measured the glomerular filtration rate in chronic experiments using other methods. The initial flows and chloride losses prior to loading on the denervated side are also greater than on the control side.

Effect of Corticotropin (ACTH) on Glomerular Permeability to Albumin and on Blood Antidiuretic Hormone Concentration in Children with the Nephrotic Syndrome. Dr. Henry D. Lauson (by invitation), Dr. Carolyn W. Forman (by invitation), Dr. Helen McNamara (by invitation), Dr. Guilherme Mattar (by invitation), and Dr. Hendy L. Barnett, New York.

Although proteinuria has long been recognized as a cardinal sign of nephrotic syndrome, the mechanism whereby protein passes from plasma to urine is still uncertain. In the present study it is tentatively assumed that increased glomerular permeability to proteins is the specific functional pathological change involved. The minimum permeability of the glomerular wall to albumin, relative to its permeability to water, is approximately equal to the albumin clearance:

inulin clearance ratio. For conveneince, the clearance of Evans blue (T-1824) may replace albumin clearance, since these have been shown by others to agree satisfactorily.

To seven children with the nephrotic syndrome and one with chronic glomerulonephritis but no edema corticotropin (ACTH) was given in daily doses of 50 to 100 mg. for 3 to 10 days. Diuresis resulted in all but one of the edematous children. In most instances inulin clearances increased. In every case the Evans-blue clearance : inulin clearance ratio decreased tenfold or more. The change in minimum permeability preceded the diuresis. Of special interest is the fact that a similar tenfold decrease in this permeability occurred in the nonedematous patient, although inulin clearance did not increase.

These decreases in minimum glomerular permeability to albumin, relative to the permeability to water, together with the increases in glomerular filtration of water, suggest that fundamental glomerular pathological change reverts toward normal with corticotropin administration. The degree of functional improvement may be a measure of the extent to which glomerular pathological change is still reversible in any given patient.

Preliminary assays were made of the antidiuretic hormone concentration of peripheral venous blood in a nephrotic child, during edema accumulation and again during diuresis following a course of corticotropin treatment. In the first observation, 75 ml. of blood were removed without emotional disturbance after 15 hours of fluid deprivation and injected immediately into a hydrated child with severe, untreated diabetes insipidus. Measurements in the recipient included urine flow, inulin and specific endogenous creatinine clearances and urine: plasma ratios, urinary total solute excretion (as approximated by the sum of the rates of excretion of urea, sodium, potassium, chloride, phosphate, creatinine, and inulin), and total concentration of the same urinary solutes. From comparison of the changes following the blood injection with changes following injection of 0.3 and 0.9 milliunits of vasopressin injection (pitressin®), the blood antidiuretic hormone concentration was estimated as equivalent to about 0.6 milliunits of vasopressin injection per 100 ml. When the assay was repeated during diuresis following corticotropin administration, 90 ml. of blood showed no antidiuretic activity when injected into the same recipient. The concentration of antidiuretic hormone must therefore have been less than 0.2 milliunits per 100 ml. of peripheral venous blood.

If confirmed, these observations suggest that the blood antidiuretic hormone concentration after a standard period of water deprivation is higher during edema accumulation than during diuresis and possibly higher than in normal subjects. This would not prove, however, that the oliguria is necessarily caused thereby. The renal tubules may already be reabsorbing an excessive fraction of the filtered water and salts because glomerular filtration is insufficient to maintain glomerulotubular balance. If so, excessive blood antidiuretic hormone concentrations would be expected to have little additional effect.

DISCUSSION

Dr. Lee E. Farr, Upton, N. Y.: This is a most interesting presentation of a very difficult and complex subject, and there are so many points on which one would wish to comment that it is difficult to select a few of the highlights for question and discussion.

It was not clear to me whether you had done Evans-blue clearances in patients with a spontaneous diuresis and whether you found changes which were similar to those after corticotropin. The question of a change in the permeability of the capillary to protein and the resultant loss of edema is intimately related to the second part of your study, in which you found that the antidiuretic factor apparently disappeared after the patients were treated with corticotropin. Did you, by any chance, offer your patients a salt challenge during the period that the antidiuretic factor was absent from the blood? Is there any way in which you can differentiate the loss of edema in these patients when this occurs by retention of plasma protein, thereby increasing the osmotic pressure, as against edema loss by the disappearance from the blood of the antidiuretic factor in large amounts? I am particularly impressed with this study of antidiuretic factor in the blood. During the past summer we made some efforts to measure the antidiuretic factor in the plasma of nephrotic patients, using the rat as the test animal and using plasma for the test substance. The difficulties of controls in this venture were so great that we could come to no certain conclusion other than that in most instances it appeared that the nephrotic child had a high level of antidiuretic factor in his plasma.

DR. JACK METCOFF, Boston: I think Dr. Lauson and Dr. Barnett's group has done a very beautiful, highly complex piece of work, as has been noted. There are several features of their work which are very interesting to all of us who have been rather interested in the nephrotic syndrome. One of these that I think is perhaps worth mentioning is the fact that decreased permeability of the glomerular membrane with a relative diminution of protein excretion should be characterized by a reduction in oncotic pressure in the urine and consequent rise in oncotic pressure in the serum. This was shown in postmeasles diuresis by Barness and Janeway some years ago. It is not entirely possible to determine whether this change is the result of diminished protein filtration and/or leakage or increased tubular reabsorption of filtered protein. The end-result would be similar. It is interesting to note that this oncotic change is also evident in corticotropin diuresis.

There are a few other things which are perhaps worthy of note. If a glomerular disease is present, or if this is a disease associated with alterations in both glomerular and tubular functions, either event provides another suggestion that this syndrome in children is one of total nephron involvement. From that point of view, some of the work in our laboratory may be of interest, in that we have been estimating, as Dr. Farr has suggested would be of some interest, combined renal hemodynamics and salt-load responses in association with both corticotropin administration and diuresis. It is interesting that there appears to be a fall in estimated total renal resistance prior to the onset of diuresis and subsequently a very large increase in efferent arteriolar resistance following diuresis. This suggests that there may be some alteration in the glomerular membrane necessitating a change in hemodynamics. At the same time, there is a marked change in the ability of the tubules to handle the sodium load. There is a large excretion of sodium at the time diuresis is starting, when the tubules are challenged with a load. Subsequently, in the nonedematous state following diuresis there appears to be a return toward the pretreatment pattern in terms of reabsorption of sodium loads. Hence, the data would suggest that the tubular defect following diuresis has not completely resolved, in that diuresis itself may not mean that the disease has been stopped. Hence, one would expect that corticotropin-treated patients may have recurrence, and this often seems to be the case.

DR. HAROLD E. HARRISON, Baltimore: Since the crux of the whole argument in this matter of glomerular permeability depends upon the demonstration that renal tubules do not reabsorb significant amounts of protein, I wish Dr. Lauson would go into a little more detail on that point.

Of course, the same results could be obtained if, after corticotropin administration, the renal tubules took up more protein and the glomerular permeability remained constant. Can that point be cleared up finally?

DR. B. M. KAGAN, Chicago: I should like to refer again, if I might, to Dr. Gitlin's work, wherein he showed in a very important way that in the nephrotic syndrome the albumin in the urine is the same as the albumin in the serum. From this he concluded or suggested that the primary or fundamental defect in the nephrotic syndrome is in the kidney. Dr. Lauson has shown us nicely that corticotropin alters the loss of protein through the kidney in the nephrotic syndrome. Dr. Kaplan and his associates have shown us that the sympathetic nervous system has an influence upon the kidney.

This prompts me to throw in a rebellious thought. We have some good evidence, though not conclusive, that the liver is functioning in an improper or abnormal way in the nephrotic syndrome and may be responsible, at least in part, for the manifestations of this syndrome. Although we know that the glucose in the urine in diabetes or in "renal" glycosuria is the same as that in the blood, we do not necessarily think that the kidney is fundamentally at fault in diabetes mellitus or in all cases of renal glycosuria. It seems to me likewise that it would be wrong—that it might defer our final solution of the problem of the nephrotic syndrome—if we adhere too strongly to the idea that the kidney is primarily at fault in diabetes mellitus or in renal glycosuria. We do not have good evidence that the pancreas is primarily at fault in all cases of diabetes mellitus, and we have evidence that the cause of "renal" glycosuria may in some cases not be in the kidney. It might help us to find the solution to the problem of the nephrotic syndrome if we keep in mind that the kidney is not necessarily the organ in which the disturbance is initiated.

DR. WILLIAM A. BRODSKY, Louisville: I should like to ask Dr. Lauson if he would amplify his remarks in connection with the last hypothesis he mentioned, namely, that part of the oliguria may be ascribed to an increased reabsorption of salt in the tubule, due, mainly, to the lowering of the filtration rate. Two of the patients presented had filtration rates of 100 and 150% of the average normal figure. Assuming the validity of a hypothesis of glomerulotubular balance with respect to salt, I should think it would be difficult to reconcile the high filtration rate with the increased reabsorption of salt observed in this syndrome.

DR. DAVID GITLIN (by invitation), Boston: I should like to try to clarify what I think are two fundamental issues at stake. When I mentioned earlier that the primary pathological defect is in the kidney, I intended to intimate only that the loss of albumin in the urine was not due to any abnormality of the serum protein, as has been suggested many times, but simply due to a defect in the kidney. I did not intend to imply that the formation of edema is due to the kidney at all.

It is entirely possible that the process for the formation of edema and the processes leading to diuresis are two separate and entirely distinct phenomena, related only as one causes or results in the materials for the accomplishment of the other. My particular views on the subject are that the marked hypoalbuminemia and the very low oncotic pressure that one gets, as shown by Dr. Janeway's group and Dr. Barnett's group, would account, by Starling's law, for the formation of edema in the periphery. Then, when the mechanism for diuresis supervenes, presumably by acting on the kidney, we have, by the formation of edema, the material necessary for a diuresis. What factors operate to maintain the principles of Starling's law in the periphery during the diuretic phase we do not know. The other part of the problem is that the retention of electrolytes and water by the kidney during edema formation may be secondary to the loss of fluid in the periphery, and thus the kidney indirectly conserves materials for the formation of the edema. Without the water with the retention of the electrolytes, we ordinarily have no edema. Consequently, I think that both problems, Starling's law in the periphery controlling edema and the mechanisms acting on the kidney controlling diuresis, are really distinct, despite their close relationship.

DR. HENRY D. LAUSON (by invitation), New York: Thank you for all these questions.

In answer to Dr. Farr, we have not made observations on changes in the dye clearance during spontaneous diuresis. However, corticotropin-induced diuresis and the spontaneous one seem to be quite similar in most respects. We did not specifically challenge the tubules by salt loading during the diuretic phase, although we always permitted the child to have a more liberal diet at that time, to avoid the possibility of collapse due to excessive diuresis.

One point that I did not have a chance to bring out is that in these antidiuretic assays, in the particular experiment itself, the clearances in the donor changed considerably between the two assays. The first time the inulin clearance was 16 cc. a minute and the second time, 37 cc. a minute; the latter was nearly normal for this child.

I want to thank Dr. Metcoff for his comments and to reemphasize the point he mentioned, that the calculation of so-called renal resistances must be interpreted with great caution in the nephrotic syndrome because there are reasons to think that permeability to water is altered. This factor is assumed to be constant in most of the calculations of resistance that I know of, and therefore they might not apply.

Dr. Kagan mentioned liver abnormalities in nephrotic syndrome. I would certainly agree there may be many, and among them probably is a hypernormal production of albumin every day to keep up with the excessive loss into the urine.

Dr. Brodsky raised the question which always comes up of how a merely mechanical reduction of glomerular filtration can of itself bring about increased reabsorption of sodium chloride and water. How does one account for edema in those not uncommon persons who have normal or even supernormal inulin clearances? This is admittedly difficult to do. The available data on this point are fragmentary, but we have had at least one observation while at Rockefeller Institute for Medical Research in which the endogenous creatinine clearance in a 2-year-old nephrotic patient was normal before and became supernormal during a spontaneous diuresis.

In the records of Dr. Barnett's group there are several instances of normal or high normal inulin clearances becoming supernormal in the process of diuresis. I have not seen the reverse occur, that is, a fall in inulin clearance at the time of diuresis.

The animal experimentation behind these remarks is now fairly convincing. The work of Shannon, of Pitts, of Selkurt, and of many others have shown this kind of phenomenon, and I think we are almost obliged to accept it as a probable underlying mechanism which may not be the most important in a given case but may be in many.

The endocrine aspects are still very unsettled. Our purpose in presenting this one experiment was twofold: first, to arouse a little interest; and, second, to show the difficulties of doing highly controlled studies of this kind from which the final answers may come.

I want to thank Dr. Gitlin for his comments. His questions refer to Starling's hypothesis of transcapillary fluid exchange. We of course do not think that Starling's hypothesis needs to be abandoned. The question of why these nephrotic kidneys provide the fluid which filters out of the capillaries to make the edema still remains.

Factors Determining Maximum Renal Water Excretion Capacity. Dr. J. D. Crawford (by invitation), Dr. E. J. Schoen (by invitation), and Dr. A. P. Nicosia (by invitation), Boston.

When urinary solute excretion is large, maximum renal capacity for water elimination is approximately 15% of glomerular filtrate volume, or about 10 cc. per square meter a minute. However, studies described in this paper show that the normal kidney cannot excrete more than 10 cc. of water per milliosmole of urinary solute. Since dissolved substances available for excretion ordinarily amount to much less than 1 milliosmole per square meter a minute, a low renal solute output may result in a marked reduction in the maximum renal capacity for water excretion. For example, persons receiving only dextrose in water may have available for excretion only 0.1 milliosmole of solute per square meter a minute and hence be able to excrete not more than 1 cc. of urine water per square meter a minute.

With the aid of studies carried out on patients with pannephritis, adrenal cortical hypofunction (Addison's disease), and nephrosis, it is shown that certain conditions also may operate to reduce this normal maximum capacity for renal water excretion. In this connection preliminary measurements of blood and urine antidiuretic hormone are presented. The importance of these observations in clinical practice is discussed.

DISCUSSION

Dr. Henry D. Lauson (by invitation), New York: I have one very brief comment. This is a beautiful demonstration throughout, but I should like to take exception to the last slide, in which concentrations of antidiuretic material were given. Half a milliunit per cubic centimeter of serum is typical of the results that have been obtained by Lloyd and all the others who have been using this rat assay for the material. I would beg you to recall that in the previous paper by direct human assay we have a value of about 0.6 milliunit in 100 cc. of whole blood. Those discrepancies are really large and should provoke interesting work in the future.

Dr. Daniel C. Darrow, New Haven, Conn.: I didn't want to say anything except that I was so glad to see somebody show what the dilution possibilities were, because I think we all realize and have realized for some time that we have been giving too much fluid to patients, as well as too little, and this will give us some measure to guide us in the future.

Dr. J. D. Crawford (by invitation), Boston: I realized that these serum levels of antidiuretic hormone would be provocative of discussion. They are not representative of antidiuretic hormone levels in the serum of the average patient. The normal person when hydrated shows no antidiuretic material in 1 cc. of serum as we do the test. This particular patient with cirrhosis has had a very high serum level and has excreted in a 24-hour urine as much as 5,000 milliunits. He is a very exceptional producer of antidiuretic hormone or antidiuretic material.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

HUMAN MILK STUDIES: XXVII. ESSENTIAL AMINO ACIDS IN HUMAN COLOSTRUM AND TRANSITIONAL MILK. SOL MILLER, VERA RUTTINGER, MARJORIE MACY RUTLEDGE, ROBERT FRAHM, SHIRLEY MAURER, ELSIE Z. MOYER, MILDRED KAUCHER, ICIE G. MACY, J. P. PRATT, and B. M. HAMIL, J. Nutrition **40**:499 (April 10) 1950.

The 10 essential amino acids were determined microbiologically in 38 samples of human colostrum and transitional milk secreted 2 to 10 days post partum. Samples were obtained from 10 women, each representing the composite mammary secretion from both breasts during 24 hours. The amino acid concentrations per 100 ml. of secretion varied with the subject and day post partum and did not parallel changes in volume of secretion or concentration of total solids. Total ntirogen and amino acid concentrations followed the same general pattern, with highest values occurring on the 5th, 6th, 7th, or 8th day post partum. The ratios between the nitrogen of the essential amino acids and total nitrogen were not consistent, indicating the possibility of shifting proportions of the casein, lactalbumin, and globulin fractions of the total protein. The same amino acids were determined in 133.6 ml. of "first" colostrum, consisting of from a few drops to 4 ml. of the first fluid from the breasts of each of 70 women, 8 to 24 hours post partum. In the "first" colostrum, values for total solids, total nitrogen, and the 10 essential amino acids were much higher than any values for human colostrum found in the literature. The percentage of total nitrogen represented by the amino nitrogen of the essential amino acids was higher than the corresponding values for the 24-hour collections of colostrum 2 to 10 days post partum. The greater percentages of amino nitrogen in the composites were accounted for by significantly higher values for arginine and threonine.

FREDEEN, Kansas City, Mo.

DETERMINATION OF SODIUM "SPACE" IN INFANTS, CHILDREN AND ADULTS. ANNE PERLEY, GILBERT B. FORBES, and MIRIAM M. PENNOYER, J. Pediat. **38**:299 (March) 1951.

Sodium "space" is described here as the volume of fluid through which Na^{24} is rapidly distributed. Thirty-seven infants and children and 19 men were studied. Time allowed for distribution of Na^{24} ranged from one and three-fourths to four and one-half hours. The data indicate that the volume of fluid occupied by sodium, in relation to body weight, declines as growth proceeds. In 11 premature infants the sodium "space" averaged 43.5% of body weight and in 16 full-term newborn infants 35.2%. In seven children from 1 to 14 years of age values averaged 30.2% and in 19 men 25.2%.

MACDONALD, Pittsburgh.

CLINICAL STUDY IN MAN OF THE EFFECTS OF VARIATION OF AGENIZED FLOUR PRODUCTS IN THE DIET. MAURICE W. LAUFER, ERIC DENHOFF, and FRANK GIUNTA, J. Pediat. **38**:341 (March) 1951.

The toxic effects of agenized flour products on animals have aroused considerable interest in the past few years. Thirty-three children were included in this study. Many had convulsions, were behavior problems, or had abnormal electroencephalograms. No toxic effects were seen after removal and reintroduction of agenized flour products into the diet.

MACDONALD, Pittsburgh.

OBSERVATIONS OF A TOTAL SERUM BASE IN CHILDREN AND YOUNG ADULTS BY A CONDUCTIVITY METHOD. W. M. KELSEY and L. B. LEINBACH, Pediatrics **4**:805 (Dec.) 1949.

Values for total serum base in 96 normal children under 12 years of age as determined by the conductivity method fell between 143 to 160.5 mEq. per liter. The mean was 153. Standard deviations for each age group are given.

The values in 73 normal persons above the age of 12 varied from 142 to 160.5 mEq. per liter. The mean was 147 mEq. per liter. A statistically significant difference between the total serum bases in children and adults was found.

FROM THE AUTHORS' SUMMARY.

MILK INDIGESTION. R. CLEMENT, Presse méd. **58**:212 (March 1) 1950.

Cow's milk is intended for the use of calves, and when it is given to human infants, digestive difficulties may arise. In general, the formula may be too strong, the fat content too high, or the infant maintained too long on an exclusive milk diet.

The first symptom of milk indigestion is alteration of the stools, the color becoming paler and the consistency more putty-like. Constipation follows, and the appetite becomes small and capricious. The weight curve flattens; the infant becomes pale and eventually anemic. Muscular hypotonia may simulate rickets, and later there may be a true rickets or tetany.

Sometimes the symptoms are more obscure. Regurgitation may be the earliest sign. Frequent stooling may occur, in spite of an adequate gain in weight, and may progress into a severe diarrhea, with invasion of the urinary tract, and even the blood, by Escherichia coli. Skin eruptions may occur.

Clement thinks that milk indigestion can be prevented by breast feeding during the first months of life, with gradual introduction of cow's milk. This is especially true in the case of the premature infant. At the first signs of indigestion, the cream should be diminished and cereal water or dextrins and maltose added. Acidification of the formula also is a useful measure.

DAFFINEE, Melrose, Mass.

PATHOGENESIS AND TREATMENT OF TOXICOSIS WITH SPECIAL REFERENCE TO TOXICITY OF INFANCY. G. FANCONI, Helvet. paediat. acta **4**:475 (Dec.) 1949.

Toxicosis in childhood can be approached from the following angles: (1) exogenous etiology, (2) special predisposition, and (3) pathogenesis of the initial phase of the illness. General therapeutic directions are given, and they are illustrated by the description of the practical treatment employed in a case of toxicosis in the Kinderspital of Zurich.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF VITAMIN B_{12} IN CHRONIC NUTRITIONAL DISTURBANCES IN INFANTS. L. SALMI, Clin. pediat. **32**:617 (Nov.) 1950.

Five hypotrophic infants showed "dramatic" improvement clinically after the administration of vitamin B_{12} (7 γ daily). Under this treatment the blood levels of protein, amino acids, iron, and cholesterol reached normal levels.

HIGGINS, Boston.

USE OF SOY BEAN AND CEREAL GERM TO SUPPLEMENT THE LOW-PROTEIN DIETS IN ITALY. R. FLUMERFELT-BALLIETTE, P. DE CAPRIO, and E. L. SEVRINGHAUS, Lattante **22**:149 (March) 1951.

Studies by the United Nations Relief and Rehabilitation Administration in Italy in 1945 revealed that the diets of Italian children were low in protein, calories, vitamins A and C, and calcium. The addition of one part of soy bean or of wheat germ to 10 parts of wheat flour afforded a cheap and useful supplement to the children's diets.

HIGGINS, Boston.

INFANT FEEDING WITH MILK DILUTED WITH VEGETABLE JUICES AND SOUPS. EMILIO BURGAS, Acta pediat. espan. **89**:541 (May) 1950.

Burgas discusses in detail the methods of infant feeding used in feeding stations and health centers, as well as in his private practice. Instead of diluting milk—cow's, goat's, powdered, or evaporated—with water, he uses the water from certain vegetables, especially carrots, beets, lettuce, spinach, green peas, and beans. This furnishes vitamins A and C. By this method he has shown that children gain much faster and have much higher resistance to the usual diseases of infancy. This is started within a few days after birth. Water from oatmeal, unpolished rice, and similar substances is also used for its vitamin B content. Later, as the child grows older, the foods are given in a strained form.

Weight tables comparing the gain in weight of a child fed in this manner with that of one fed the more usual diet are included, as well as charts comparing the incidence of infections in the two groups of children. For children severely malnourished the author advises, as an

adjunct to this feeding, thiamine in a commercial preparation by the third month and liver soup or other liver products by the fourth month. This procedure is a simple, inexpensive, and safe way to add vitamins and minerals to the baby's diet.

ALLEN, Santa Fe, N. M.

PARENTERAL HUMAN MILK THERAPY AND PROPHYLAXIS: PROCEEDINGS OF THE SOCIETY OF PHYSICIANS IN VIENNA. A. SOLE, Wien. klin. Wchnschr. **63**:370 (May 18) 1951.

Mother's milk obtained under sterile precautions is tolerated without reaction on parenteral administration. Daily injections of 15 ml. of human milk over a period of two weeks are recommended for the treatment of chorea.

AMBERG, Rochester, Minn.

POTASSIUM STUDIES IN PEDIATRIC DISEASES (PYLORIC STENOSIS, RENAL FAILURE, AND DIABETIC ACIDOSIS). T. S. DANOWSKI, L. GREENMAN, J. H. PETERS, E. A. WEIGAND, H. A. MERMELSTEIN, W. B. PARSONS, and F. M. MATEER, Acta pædiat. **40**:198 (May) 1951.

Some of the results of potassium studies in infants with pyloric stenosis, in children with renal failure, and in juvenile diabetics treated for acidosis or coma have been presented by means of illustrative cases. Mechanisms involved in potassium transfers in these situations have been discussed.

FROM THE AUTHORS' SUMMARY.

Vitamins; Avitaminoses

VITAMIN A UTILIZATION STUDIES: III. THE UTILIZATION OF VITAMIN A ALCOHOL, VITAMIN A ACETATE AND VITAMIN A NATURAL ESTERS BY HUMANS. ERLING F. WEEK and FRANK J. SEVIGNE, J. Nutrition **40**:563 (April 10) 1950.

Under normal conditions the greater proportion of the vitamin A in human serum was present in the alcohol form. However, after the ingestion of 134,000 μg. of the vitamin, the increased vitamin A in the serum was present as the ester, irrespective of the chemical form of the vitamin administered in the supplement.

FREDEEN, Kansas City, Mo.

RACHITOGENIC REGIMENS. J. CATHALA and F. VERLIAC, Presse méd. **57**:1097 (Nov. 30) 1949.

In a long and scholarly treatise, the authors point out that the origin and the treatment of rickets are too complicated to be easily understood. The cause is not entirely dietetic, and the cure does not lie in adjusting the calcium-phosphorus ratio. Experimental evidence is cited to show the role played by varying amounts of calcium, phosphorus, vitamins, acidosis, and alkalosis. Rickets produced by a high calcium-phosphorus ratio is made worse by the addition of other mineral salts, particularly metallic carbonates. The effects of an unbalanced mineral metabolism can be wiped out by the addition of an acid to the diet such as lactic acid, but rickets can be produced with an acidotic regimen. Cow's milk has more calcium and phosphorus than mother's milk—yet it is likelier to produce rickets. An excess of cereal can cause rickets, from its decalcifying properties. Indigestion from gastric causes or intestinal insufficiency can also produce rickets.

Even when all the dietetic and digestive abnormalities are corrected, other factors in the life of the patient must be harmonized. The general home hygiene, family relationships, and the whole impact of the environment have so much to do with growth and development that correction of substandard conditions must be undertaken in the treatment of rickets.

DAFFINEE, Melrose, Mass.

HISTOLOGICAL STUDY OF THE OSTEOID TISSUE IN RICKETS. F. CARLOSTELLA, Minerva pediat. **2**:597 (Dec.) 1950.

After reviewing and demonstrating by illustrations the development of the present day knowledge of osteoid tissue, the author draws the following conclusions: The two typical phenomena of rickets consist in (1) the abnormal formation of cartilaginous into connective tissue and (2) the body's incapacity to calcify this preosseous tissue. These phenomena result in the lawless behavior of the tissues at the epiphyses seen in rickets.

HIGGINS, Boston.

Hygiene; Growth and Nutrition; Public Health

SEX FACTOR IN EARLY DEVELOPMENT. M. SCHACHTER and S. COTTE, Lattante **22**:144 (March) 1951.

In Marseilles, France, a study of the development of 522 boys and 310 girls revealed that dentition and walking began sooner in boys, as a rule, while talking and bladder control occurred sooner in the girls.

HIGGINS, Boston.

DEVELOPMENT OF THE ITALIAN CHILD IN THE POSTWAR PERIOD: (1949). V. BACCHETTA, Minerva pediat. **3**:9 (Jan.) 1951.

This paper covers some of the findings of Professor Frontali's investigation, sponsored by the United Nations International Children's Emergency Fund.

Children in northern and central Italy have shown in 1949 a 5% greater height and 13% greater weight than children of the same age in 1945. In southern Italy the children were found to be about 1% taller and 3% heavier on the average in 1949 than in 1945. In Sardinia, however, the children were on the average of the same height and weight in 1949 as in 1945. More food and better food are certainly largely responsible for the larger and healthier children of the postwar period.

HIGGINS, Boston.

BODY GROWTH AND STRUCTURE. M. BARBARA, Minerva pediat. **3**:13 (Jan.) 1951.

This article gives an outline of the approach of the Genoa School of de Toni in classifying the various types of body structure; this scheme and nomenclature are widely used in Italy.

HIGGINS, Boston.

A SIMPLE GRID IN EVALUATING THE GROWTH OF CHILDREN. G. DE TONI, Minerva pediat. **3**:83 (Feb.) 1951.

This grid allows the plotting of a child's height and weight expressed in the amount of deviation from normal weight and height for age.

HIGGINS, Boston.

NEW MEANS FOR COMBATING THE CAUSE OF INFANT MORTALITY. P. RITOSSA, Pediatria **59**:165 (March) 1951.

The infant mortality rate is over twice as high in Italy as in the United States, Switzerland, and England and appreciably higher than in France and Spain. In lowering this high rate, especial attention must be given to prophylaxis and therapy in the field of infections in infants.

HIGGINS, Boston.

INFANT MORTALITY IN THE FIRST YEAR OF LIFE DURING AND AFTER THE WAR IN THE COMMUNE OF FLORENCE. ALESSANDRO BIEBER, Riv. clin. pediat. **49**:271 (April) 1951.

Bieber gives a review of infant mortality before, during, and after the war (1930-1949) in the city of Florence.

FROM THE AUTHOR'S SUMMARY.

ANTHROPOLOGY OF GROWTH: SOME DATA FOR THE STUDY OF PHYSICAL DEVELOPMENT OF THE SPANISH CHILD. GREGORIO MARINA BOCANEGRA, Acta pediat. españ. **90**:681 (June) 1950.

This is a study of anthropometric measurements made on 684 newborn children. No premature or evidently sick children or children with anomalies were included. Measurements were made at monthly intervals, and these are given on various charts. The figures given were weight, height, and cephalic and thoracic circumferences.

Similar studies in other countries are compared. There is an appreciable difference in weight and length of the newborn in Spain, France, and Italy as compared with those in the United States and Germany. However, this difference is somewhat less by the time the child reaches one year of age, although the rate of growth will continue to be different in Latin and Anglo-Saxon countries. The writer points out that the weight at any given age should never be represented as a single number, but that the normal zone of growth with minimum and maximum figures should be clearly evident.

ALLEN, Santa Fe, N. M.

VALUE OF THE VITAL COEFFICIENT OF SPEHL. JUAN ANTONIO RUIZ SANTA MARIA, Acta pediat. españ. **90**:693 (June) 1950.

The author, a school physician, believes that the vital coefficient of Spehl should not be overlooked or minimized in examinations of school children. The formula is the following: vital coefficient = vital capacity × weight/height. The details of weight and height measurements and of the use of the Wintrisch spirometer are given, as well as a discussion of breathing exercises. The author concludes that the male students have a higher vital coefficient except in the prepuberal period and that it has a direct relation to muscular exercise and increases in cases in which exercise and work involving muscles are part of the child's occupation.

Schools should encourage children to do rhythmic exercises and breathing exercises through both the nose and the mouth. This should be compulsory except for children who have some illness which would exempt them. The vital coefficient is an index of the child's robustness and a help to other means of natural defense against disease.

ALLEN, Santa Fe, N. M.

THE NUTRITIVE STATE OF THE CHILD AND THE LIVING CONDITIONS IN ITS FAMILY GROUP. ALBERTO DUARTE GONZALEZ, WERNER BUSTAMANTE ESPINOZA, and V. S. FRIEDA PUEBLA LEESON, Rev. chilena pediat. **22**:119 (March) 1951.

Two groups of families, one with eutrophic children and the other with dystrophic children, followed in the Maternal and Child Protective Center for a period of two years, were studied concerning their economic, cultural, health, and social circumstances. A comparison of the data for the two groups of families revealed that the standard of living is much lower in the family with a dystrophic child. The medicosocial factors in a family must be taken into account in any program of pediatric welfare services for effective treatment and prevention of dystrophy.

FROM THE AUTHORS' SUMMARY.

ANTHROPOMETRIC CONSTITUTION PROGNOSIS FROM CHILD TO ADULT. FREDERICH KEITER, Deutsche med. Wchnschr. **76**:666 (May 18) 1951.

Various anthropometric measurements or indices were determined in 200 mother-child pairs. The conclusion is reached that the individual somatic constitution as expressed by these measurements is well developed in childhood, so that the growth proceeds along a well-determined plan. The paper should be consulted for greater detail.

AMBERG, Rochester, Minn.

Prematurity and Congenital Deformities

HISTOLOGICAL EFFECTS ON THE EMBRYO FOLLOWING X-IRRADIATION. ROBERTS RUGH, J. Morphol. **85**:283 (Nov.) 1949.

Larvae of Amblystoma punctatum (2.2 cm. total length) were given a single dose of 15,000 r of x-rays and were allowed to live one week before they were killed and prepared for study of the histological and cytological changes.

The tissues most resistant to x-ray damage were cartilage and muscle. There was no evidence of damage to the matrix of the cartilage or to the myoplasm or myofibrillae of the muscle.

The central nervous system tissue and its related sense organs were most sensitive to x-ray damage. Neuroblasts were sloughed off into the brain cavity, and cells and nuclei were in all stages of degeneration. There was no evidence of growth. This tissue was the most actively differentiating type at the time of irradiation.

The larval or embryonic tissues are variously sensitive to x-ray damage, but in a manner quite different from the adult tissues.

The discussion considers the possibility that the so-called resting (premitotic or postmitotic) cell is more severely damaged than the more obvious mitotic phases, since there was complete inhibition of mitoses in all nonmitotic cells.

REID, New Brunswick, N. J. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ILLNESS IN THE FIRST TRIMESTER OF PREGNANCY: ITS LACK OF SIGNIFICANCE IN RELATION TO CONGENITAL ANOMALY OF THE OFFSPRING AND TO FULL-TERM PREGNANCY, PREMATURITY, AND STILLBIRTH. EVELYN E. HARTMAN and ROGER L. J. KENNEDY, J. Pediat. **38**:306 (March) 1951.

In the group reported here, 148 mothers were ill in the first trimester of pregnancy. These mothers subsequently bore 149 children, 8 of whom (5.4%) had congenital abnormalities. In 1,088 infants whose mothers were not ill in the first trimester, the rate of congenital abnormalities was 5.2%. Furthermore, illness in the first trimester had no apparent effect on the incidence of full-term pregnancy, prematurity, or stillbirth.

MACDONALD, Pittsburgh.

AN ACCESSORY BONE AND OTHER BILATERAL SKELETAL ANOMALIES OF THE ELBOW. W. A. SIMRIL and MILDRED TROTTER, Radiology **53**:97 (July) 1949.

The authors describe a rare osseous structure which they discovered anterior to the elbow joints in a cadaver with extensive hypertrophic arthritic changes. These ossicles were intracapsular but free from the capsule; and they were not embedded or intimately associated with a tendon. These findings eliminate its classification as sesamoid. The authors do not agree with those who consider the presence of an accessory bone of the elbow to be invariably the result of trauma. "Os cubiti anterius" is suggested as a name for this unusual bone, which is reported as a true anomaly. A transverse ridge of bone in the olecranon fossa was found bilaterally in the same cadaver and is reported as a second anomaly.

ANSPACH, Chicago.

ROENTGENOLOGIC PICTURE OF THE VERTEBRAL COLUMN OF THE PREMATURE INFANT. L. MARTONI, Clin. pediat. **33**:101 (Feb.) 1951.

The vertebrae of the premature infant appear narrower than the intervertebral spaces in the lower dorsal and lumbar regions; they are only slightly wider than the interspaces in the cervical, the upper dorsal, and the sacral regions.

HIGGINS, Boston.

PIGMENTARY DYSTROPHY AND SEGMENTAL MALFORMATION IN CHILDREN. M. SCHACHTER, Clin. pediat. **33**:137 (March) 1951.

Two children, 8 and 14 years of age, had many large brown-pigmented areas over their bodies; these were not hairy moles, nor were they elevated as in molluscum. One of the children was very large for his age, obese, mentally retarded, and had bilateral optic atrophy; his father had similar pigmented spots over his body. The other child was definitely retarded physically and sexually and had a congenital dystrophy of the left arm, a segmental malformation. This pigmentary abnormality seems to be a manifestation of a hereditary, constitutional, pituitary syndrome.

HIGGINS, Boston.

BIOMETRIC AND MENTAL STATUS OF A BOY OF 19 YEARS WHO HAD BEEN A PREMATURE INFANT WEIGHING 600 GRAMS. M. BERNARDI, Minerva pediat. **3**:22 (Jan.) 1951.

This boy, born a premature baby of 600 gm., now has an intelligence quotient of 85, is socially well adjusted, but is rather small, weighing 43 kg., and being 151 cm. tall. His anthropometric measurements at the ages of 7 and of 19 years are recorded.

HIGGINS, Boston.

SPRENGEL'S DEFORMITY. E. KRATKOVÁ, Pediat. listy **5**:105 (No. 2) 1950.

Two cases of congenital high scapula (Sprengel's deformity) in children with many other deformities of the skeleton are described. One of the cases is a rare combination, with complete aplasia of the internal ear.

FROM THE AUTHOR'S SUMMARY.

Newborn

ASPHYXIA NEONATORUM AND THE VERNIX MEMBRANE. FRED DICK JR. and EDGAR R. PUND, Arch. Path. **47**:307 (April) 1949.

The authors wish to emphasize the importance of aspiration of vernix caseosa with resulting asphyxia as a primary cause of death in liveborn infants. Material from 119 consecutive autopsies

on liveborn and stillborn infants who died during the years 1938 to 1947 was examined. In addition, the authors conducted experiments to produce a membrane in the alveoli of several stillborn autopsied lungs, using the sediment of centrifuged specimens of amniotic fluid. The attempts were unsuccessful, and the authors attributed their failure to material low in lipids.

These results, the authors feel, lend support to their theory, namely, that only with concentrated vernix, high in lipid content and present in increased amounts in the respiratory tract and alveoli before birth, can the characteristic fatty hyaline membrane be produced. Thus with the first extrauterine breath, the material is forced against the alveolar walls and ducts. As respiration becomes more forceful, greater expansion takes place and more vernix is aspirated into the smaller units from above. The authors believe that pneumonia, if present, prepares a fertile field for the development of the membrane, owing to the increased stickiness of the walls. The resulting asphyxia leads to characteristic symptoms in those infants living up to the age of 4 days. They may breathe normally or be slow to breathe at birth, but eventually dyspnea and cyanosis develop in spite of oxygen and carbon dioxide insufflation. Costal retraction may be present. The authors advocate immediate aspiration of the upper air passages after delivery, to forestall more extensive involvement of the lungs in those cases in which vernix caseosa is not present beyond the tracheal bifurcation.

HAW CHAN, San Francisco.

MULTIPLE CYSTIC SOFTENING OF THE BRAIN IN THE NEWBORN. C. E. LUMSDEN, J. Neuropath. & Exper. Neurol. **9**:119 (April) 1950.

Interpretation of some of the problematical cases of infantile encephalomalacia in the literature is rendered difficult because there is no clear-cut information regarding the presence or absence of injury to the brain at birth.

Lumsden reports a case of "disseminated encephalomalacia with multiple cavity formation." There was no history of cerebral birth injury or of asphyxia neonatorum, and careful anatomical study disclosed no vascular injury or thrombosis.

The author gives reasons for rejecting Marburg and Casamajor's hypothesis that these, and allied, forms of encephalomalacia (including Schilder's disease, or progressive subcortical encephalopathy) in the newborn and in young infants are due solely to phlebothrombosis and phlebostasis in the Galenic system and are caused by cerebral birth injury. He draws attention to the possible role of transsynaptic degeneration and the much greater ferment activity in the production of malacia in degenerative disease of the central nervous system of the infant.

The suggestion is offered, from this study, that damaged myelin itself liberates a lytic ferment, the activity of which, in most pathologic processes, is neutralized or checked in some way by the action of the oligodendroglia. If the oligodendrocytes were primarily diseased or defective, the inhibitory action of these cells upon the myelin ferment might be lost or impaired, so that myelinolysis could spread relatively unimpeded. Such a mechanism could account for the specific histopathologic features of the primary demyelinating diseases.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ERYTHEMA MULTIFORME AS A MANIFESTATION OF NEONATAL SEPTICEMIA. HAROLD J. STARR and POPE B. HOLLIDAY JR., J. Pediat. **38**:315 (March) 1950.

Erythema multiforme is a syndrome that probably represents an allergic response to a variety of allergens. Starr and Holliday report three newborn infants with this syndrome associated with septicemia.

MACDONALD, Pittsburgh.

A SURVEY OF THE RH PROBLEM IN MIXED RACIAL GROUP. HERBERT H. POMERANCE and LOUIS J. SALERNO, J. Pediat. **38**:349 (March) 1951.

The material was 3,011 pregnancies; the group was made up of 582 white, 1,301 Negro, and 1,128 Puerto Rican women. The rates for Rh-negative women were 15.6% in white women, 11.4% in Negroes, and 12.8% in Puerto Ricans. The incidence of hemolytic disease of the newborn was 1:116 white births, 1:434 Negro births, and 1:1,128 Puerto Rican births.

MACDONALD, Pittsburgh.

RICKETS IN NEWBORN AND PREMATURE INFANTS: CLINICAL AND HISTOLOGIC STUDY. STIG RANSTROM and GERT VON SYDOW, Pediatrics **4**:406 (Oct.) 1949.

In a series of 181 consecutive infants who had died soon after birth, 103 (56.9%) showed definite histologic signs of rickets. Of the 69 infants dying during the first day of life, 20 (29%) had rachitic changes, and in these the rickets must be regarded as congenital. Of the 181 infants, 154 were premature, weighing less than 2,500 gm. at birth. The incidence of rickets was about the same in the premature and the full-term infants. The incidence of rickets increases rapidly with increasing age during the first weeks of life.

FROM THE AUTHORS' SUMMARY.

ESSENTIAL THROMBOCYTOPENIC PURPURA IN THE NEWBORN. SEYMOUR S. BLUESTONE, Pediatrics **4**:620 (Nov.|) 1949.

A case of thrombopenic purpura in a newborn infant is reported. It is one of the few cases in which the mother of the patient did not herself have this disease. It is believed to be the first case in which a newborn infant was treated by splenectomy. Observations are made which aid in the selection of such cases for surgery, and which, incidentally, lend support to the humoral theory of the pathogenesis of the disease. A newborn infant with thrombopenic purpura may be expected to benefit from splenectomy, providing the usual indications exist, only if the mother is herself free of the disease.

FROM THE AUTHOR'S SUMMARY.

FATAL BORIC ACID POISONING IN A NEWBORN INFANT. HAROLD ABRAMSON, Pediatrics **4**:719 (Dec.) 1949.

A case is reported of fatal boric acid poisoning in a 9-day-old baby. This chemical was applied as an ointment to a large excoriated area of the baby's buttocks and as a powder on the diapers. The history was that of diarrhea and dehydration and bullous skin lesions. Postmortem examination showed hemorrhages in the kidneys and intestines. Fresh specimens of the intestine and liver and pieces of the brain, liver, and kidneys preserved in formaldehyde were analyzed. Boric acid was found in the amount of 26 mg. in 50 gm. of composite sample, or 0.052%. This quantity represents a lethal concentration of boric acid in the tissues.

It is suggested that boric acid should be discarded in medical practice, since its potential toxicity represents a hazard that is out of proportion to the doubtful therapeutic value of the drug. Boric acid has been outmoded by more effective modern medications.

FROM THE AUTHOR'S SUMMARY.

STUDIES OF THE CARDIOVASCULAR AND RENAL SYSTEMS IN THE NEWLY BORN INFANT USING FLUORESCEIN: I. CIRCULATION TIME IMMEDIATELY AFTER BIRTH. LAWRENCE SLOBODY, GEORGE ROOK, MORRISON LEVBARG, and MADELAINE MORCY, Pediatrics **6**:254 (Aug.) 1950.

One of the physical characteristics of fluorescein is the emission of a greenish-gold fluorescence when exposed to long wave ultraviolet light. Circulation times were determined in newborn infants by injecting fluorescein solution through a polyethylene tube which had been placed in the umbilical vein in 45 cases and in the ductus venosus in another 45 cases. The time was calculated from the moment of injection of the fluorescein to the appearance of the fluorescence in the lips of the subjects when observed under the long wave ultraviolet lamp.

The mean circulation time from umbilical vein to lip was 4.8 ± 0.7 seconds, with a range of 3.1 to 7.0 seconds. The mean circulation time from ductus venosus to lip was 4.4 ± 0.6 seconds, with a range of 3.3 to 5.8 seconds. It is recommended that 0.1 ml. of a 5% fluorescein in 5% sodium bicarbonate solution and polyethylene tubing of 0.047-in. (1.6 mm.) internal diameter be used. This determination is simple and accurate and may aid in the differential diagnosis of cyanosis of the newborn infant.

FROM THE AUTHORS' SUMMARY.

OSSEOUS CHANGES IN ERYTHROBLASTOSIS FETALIS. WILLIAM JANUS and M. WENDELL DIETZ, Radiology **53**:59 (July) 1949.

Erythroblastosis develops in the fetus of Rh-negative mothers because of the development of an abnormal agglutinin in the serum of the mother; passage of this diffusible substance into the fetal circulation results in destruction of erythrocytes and the production of typical clinicopathological syndrome.

In roentgenograms of eight of the authors' 17 patients transverse lines of increased density in the juxtaepiphyseal portions of the shafts of bones were present. These changes result from a transient disturbance of endochondral bone formation. The authors describe similar changes due to other conditions, such as prematurity, chronic maternal illness, and infantile syphilis. The radiopaque bands seen in a high percentage of roentgenograms are significant though not diagnostic of erythroblastosis; absence of them in no way invalidates the clinical and laboratory diagnosis of the disease.

ANSPACH, Chicago.

NEURO-MUSCULAR INCOORDINATION AT THE CARDIA IN THE NEWBORN. JOHN THOMSON, Arch. Dis. Childhood **25**:52 (March) 1950.

Two cases of achalasia of the cardia in the newborn infant are reported, and the literature on achalasia of the cardia in the newborn is reviewed. A case of vomiting of doubtful origin in the newborn infant is described. Consideration is given to a diagnosis of excessive relaxation of the cardia, achalasia.

KELLY, Milwaukee.

HAEMOLYTIC DISEASE OF THE NEWBORN: PART I. A CLINICAL-PATHOLOGICAL STUDY OF 157 CASES. ALBERT CLAIREAUX, Arch. Dis. Childhood **25**:61 (March) 1950.

This study deals with the features presented by 157 cases of hemolytic disease of the newborn, including 36 cases of hydrops fetalis, 110 of icterus gravis, and 11 of hemolytic anemia. The pathological changes found in all forms of the disease are noted. The obstetrical histories of the mothers of the affected infants were investigated and various factors of prognostic significance examined. The clinical features of the affected patients and the criteria of severity were similar to those reported by other workers. An unusual feature was the severity of the disease process in 10 women who were pregnant for the first time.

KELLY, Milwaukee.

HAEMOLYTIC DISEASE OF THE NEWBORN: PART II. NUCLEAR JAUNDICE (KERNICTERUS). ALBERT CLAIREAUX, Arch. Dis. Childhood **25**:71 (March) 1950.

The clinical and pathological features of 37 cases of nuclear jaundice occurring among 110 patients with severe icterus neonatorum are described. Twenty-eight of these 37 patients died by the end of the first week of life. Only four survived the neonatal period, and only two were alive at the time of writing. The histological changes present in the brain in nuclear jaundice are described in detail, and an attempt is made to explain the development of the condition on the basis of these histological findings.

The prognosis in nuclear jaundice is exceedingly grave both as to the immediate chances of survival and as to the future development of the affected child. It is too early to judge the effect of modern methods of transfusion therapy.

KELLY, Milwaukee.

EPULIS IN THE NEWBORN. F. A. LANGLEY and J. DAVSON, Arch. Dis. Childhood **25**:89 (March) 1950.

Three cases of congenital epulis in infants are described. The tumors consisted of large round or polyhedral granular cells separated from one another by a fine reticulum. Twenty-three similar tumors previously described are briefly reviewed. The theories of origin of these tumors —muscle, misplaced dental anlage, basal epithelium, and lymphatic endothelium—are briefly discussed. None appears to be adequate. It is suggested that these congenital granular tumors are mesenchymal in nature.

KELLY, Milwaukee.

Acute Contagious Diseases

SELECTIVE DESTRUCTION OF LARGE MOTONEURONS BY POLIOMYELITIS VIRUS: II. SIZE OF MOTONEURONS IN THE SPINAL CORD OF RHESUS MONKEYS. ROBERT HODES, SAMUEL M. J. PEACOCK, and DAVID BODIAN, J. Neuropath. & Exper. Neurol. **8**:400 (Oct.) 1949.

The authors studied the size and distribution of the motoneurons of the anterior horns of six normal monkeys and of three animals in the chronic stage of experimentally induced polio-

myelitis. They found that spinal cords from the infected animals showed a greater proportion of small neurons and a smaller proportion of large cells than did normal cords. The relative preponderance of small motoneurons and the paucity of large nerve cells increased with the severity of the lesion.

The authors believe that the abundance of small motor cells and the scarcity of large motoneurons is due to the fact that the virus of poliomyelitis first singles out for destruction the large motoneurons of the population and leaves relatively intact the small cells. As the disease process increases in intensity, small motoneurons are also destroyed.

This selection for destruction of large neurons in preference to small ones is known to occur in other pathologic processes, e. g., amyotrophic lateral sclerosis (Wohlfart and Swank) and chronic thiamine deficiency (Swank). Simple physical changes and mechanical effects, such as pressure or surgical manipulation (Hard and Lassek), are but a few of the agents whose harmful effects are seen chiefly on nerve cells of a particular size. The present study makes available additional data for the investigation of an important biologic question, namely, the fundamental basis for selective size-linked susceptibility of a neuron to a variety of diverse harmful agents.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

INFLUENCE OF INFECTION WITH LANSING STRAIN POLIOMYELITIS VIRUS ON PREGNANT MICE. C. L. BYRD, J. Neuropath. & Exper. Neurol. **9**:202 (April) 1950.

Baker and Baker observed that acute poliomyelitis is more frequent in pregnant women than could be attributed to mere chance or random sampling. The course of the disease in pregnancy does not differ from that in nonpregnant women or in males, but 30.4% of the pregnant women who contract poliomyelitis abort.

Mice are frequently used in experiments with the virus of poliomyelitis, especially for the study of Lansing-type strains. Byrd attempted to ascertain whether mice react similarly to infection with mouse-adapted poliomyelitis virus during pregnancy.

Inoculation with the Lansing poliomyelitis virus was carried out on 227 pregnant mice and an equal number of nonpregnant controls. The disease had a shorter incubation period and caused a high number of abortions in pregnant mice.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MEASURE OF IMMUNOLOGIC RESPONSES TO AN IMPROVED PREPARATION OF DIPHTHERIA AND TETANUS TOXOIDS (ALUM PRECIPITATED) COMBINED WITH PERTUSSIS VACCINE. RALPH M. TYSON and BERNARD J. HOUSTON, J. Pediat. **37**:357 (Sept.) 1950.

The material used in this study contained less than 10 mg. of alum in each dose. One complete treatment consisted in three 0.5 cc. injections, totaling two human doses each of diphtheria and tetanus toxoids and 45,000,000,000 Hemophilus pertussis organisms. Injections were given at monthly intervals, starting at 5 to 6 months of age. As measured by skin tests and blood titers, this material provides adequate protection for the three diseases. No serious local or systemic reactions to injections were observed.

MACDONALD, Pittsburgh.

MANAGEMENT OF RESPIRATORY FAILURE IN ACUTE POLIOMYELITIS. RICHARD W. MAXWELL, JOSEPH MUENSTER, and ROBERT F. L. POLLEY, Northwest Med. **50**:425 (June) 1951.

This is an article based on the authors' experience with 168 patients with acute poliomyelitis admitted to the isolation division of the St. Louis City Hospital in 1949. Institution of an energetic prophylactic program as opposed to conservatism has resulted in a decrease in the mortality and morbidity rates at this institution. As regards the potentially anoxic poliomyelitis patient, the program as outlined includes the following: (1) immediate oxygen tent, (2) Trendelenburg position, (3) suction of the upper respiratory tract, (4) Wangensteen gastric suction, (5) correction of dehydration and acidosis, (6) early tracheotomy, (7) delivery of humidified oxygen by tracheotomy orifice, and (8) respirator. The importance of early tracheotomy and the use of cold steam and oxygen therapy are stressed. Statistics are presented which bear out the conclusions of the authors.

DOCTOR, Seattle.

MINUTE ABSORPTION OF DIPHTHERIA ANTIBODIES FROM THE GASTROINTESTINAL TRACT IN INFANTS. BO VAHLQUIST and CURT HOGSTEDT, Pediatrics **4**:401 (Oct.) 1949.

Human serum rich in antibodies against diphtheria was given orally to newborn and to older infants. With few exceptions, an absorption of antibodies could be traced only in the first week of life and even then only in minute amounts (< 0.30 of the total antibody amount administered). The implications of these findings for the value of human milk as an antibody source are discussed.

FROM THE AUTHORS' SUMMARY.

PERTUSSIS DUE TO BRUCELLA BRONCHOSEPTICA: CASE REPORT. CHANG SHIHMAN, Pediatrics **6**:227 (Aug.) 1950.

A case clinically resembling pertussis and due to Brucella bronchiseptica is reported.

FROM THE AUTHOR'S SUMMARY.

MUSCLE SPASM IN POLIOMYELITIS: A STUDY OF A NEW ZEALAND EPIDEMIC. J. E. CAUGHEY and D. S. MALCOLM, Arch. Dis. Childhood **25**:15 (March) 1950.

Muscle spasm is found in all patients with poliomyelitis. It may be present at rest and is increased by stretching. It may resolve, or a muscle so affected may pass into a state of flaccid paralysis or into a state of contracture.

Electromyographic studies have failed to demonstrate electrical potentials in muscles in a state of spasm. Increased sensitivity or hyperirritability of the stretch reflex is present.

Spinal anesthesia relieved spasm in the acute stage of the illness but not in the chronic stage. Curare failed to relieve spasm in the acute stage of the illness.

Concerning the acute phase of poliomyelitis, the authors believe that the muscle spasm is in part the result of reflex spasm due to meningeal inflammatory changes irritating the pain-sensitive structures of the meninges and dorsal roots, and in part due to a local lesion in the muscles themselves.

KELLY, Milwaukee.

PARALYSES FOLLOWING IMMUNISING INJECTIONS. GUY BOUSFIELD, Lancet **1**:1028 (May 12) 1951.

Bousfield reports that poliomyelitis seems to occur much less often in the first months of life than in the next few years of childhood. As the risk of postinjection poliomyelitis is probably proportional to the lability to contraction of the disease, he suggests that immunization against diphtheria should be undertaken at about the age of 2 to 5 months. He shows that infants can be immunized successfully at this age and that in the great majority the immunity holds good some 18 months to 2 years later. Active immunity was obtained in 98.9% of Schick-positive infants by the sixth or seventh month of life. He found that the diphtheria prophylactics are best given subcutaneously and he believes the intramuscular route should be avoided.

MADOW, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

POSTVACCINAL NEPHRITIS. J. F. PORGE, Presse méd. **58**:320 (March 25) 1950.

The author calls attention to the appearance of renal reactions to any vaccine or toxin derivative. These reactions are likelier to occur if the subject shows albuminuria or has had kidney disease. Allergy is probably the basic cause of the reactions.

DAFFINEE, Melrose, Mass.

NEUROVEGETATIVE DISTURBANCES IN POLIOMYELITIS. HANS ZELLWEGER, Helvet. paediat. acta **5**:195 (June) 1950.

A rise in blood pressure is frequently observed during the acute inflammatory phase of anterior poliomyelitis, whether it be the lighter meningitic form, the severe spinal paralytic form, or the bulboencephalitic form of the disease. As a rule, it is merely a transitory rise in blood pressure, which subsides again after a few days. It is thought to be due to involvement of the blood-pressure-regulating center by the poliomyelitic process.

Zellweger reports two cases of poliomyelitis associated with acrodynia. In one case the two afflictions were present simultaneously; in the other acrodynia developed 10 weeks after the onset of poliomyelitis.

Another case is described in which there was evidence of more disseminated affection of the autonomous nervous system, as was shown by the following symptoms: hypertension, emotional instability, trophic ulcers, retention of urine, and constipation; and one case is reported because of an isolated lesion of the vagus nerve.

One case is described in which adiposogenital dystrophy developed four years after the patient suffered from a severe attack of paralytic poliomyelitis. The author discusses the possible etiological connection between these two conditions, but he is prepared to recognize only a partial link.

FROM THE AUTHOR'S SUMMARY.

KIDNEY IN DIPHTHERIA. BRUNO GARAU, Ann. ital. pediat. **3**:373 (Aug.) 1950.

The author studied the microscopic and histologic changes in kidneys of 28 children who died of diphtheria between the ages of 2½ months and 4 years. The principal change observed in all cases was nephrosis, usually necrosis of the epithelia of twisted tubules.

The author stresses the notable frequency of renal inflammatory complications in diphtheria: in 10 cases (35.71%) inflammatory changes were present (eight cases of glomerulonephritis and two cases of interstitial nephritis).

FROM THE AUTHOR'S SUMMARY.

CULTIVATION OF THE VIRUS OF POLIOMYELITIS. D. GOTTI, Clin. pediat. **33**:126 (Feb.) 1951.

The author has been able to cultivate on chick embryo the virus of poliomyelitis, obtained from the spinal cord of cats which had been inoculated with the infectious material of a patient with the disease.

HIGGINS, Boston.

TONSILLECTOMY AND POLIOMYELITIS. E. PIRODDA and G. RAIMONDI, Lattante **22**:129 (March) 1951.

The histories of 4,000 children from the cities of Bologna, Calgari, Milan, and Florence who had acute poliomyelitis in the years 1940 to 1949 were reviewed to learn if there had been a tonsillectomy performed shortly before the onset of the disease. Ten children (0.25%) had had a tonsillectomy shortly before the attack of poliomyelitis; nine cases were of the spinal type of poliomyelitis and only one was bulbar. Although the data do not prove a specific relationship between tonsillectomy and poliomyelitis, especially of the bulbar type, postponement of tonsillectomy until after an epidemic is over is recommended.

HIGGINS, Boston.

CLINICAL STATISTICS AS TO THE COMPLICATIONS OF SCARLET FEVER IN THE YEARS 1911 to 1949, AS AFFECTED BY METHODS OF THERAPY AND THE NATURE OF THE INDIVIDUAL EPIDEMIC. G. BUCCELLATO and N. CAROLLO, Pediatria **59**:75 (Jan.) 1951.

In Palermo, Sicily, severe epidemics of scarlet fever occurred in the years 1917 and 1925 to 1932; there were many complications and a mortality rate of 32 to 55% among patients admitted to the clinic. A more recent epidemic in 1949 was very mild, with only rare complications and a mortality rate of 1.8%.

HIGGINS, Boston.

PROPHYLAXIS OF MEASLES WITH GAMMA GLOBULIN. ROANO ROSSI, Riv. clin. pediat. **48**:305 (May) 1950.

The findings previously reported in the literature on the prophylactic action of gamma globulin in measles have been confirmed by Rossi. He is therefore favorable to their use, even if it is restricted to specific cases.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

PARALYSIS FROM TETANUS ANTITOXIN. L. B. DAVIS, J. Nerv. & Ment. Dis. **113**:61 (Jan.) 1951.

In a white youth aged 18, who was free from ordinary allergies and who showed no unusual response to intradermal testing, serum sickness developed one week after an injection of tetanus antitoxin. He experienced persistent pain in the right shoulder, and there soon developed weakness of the scapular and shoulder muscles supplied by the fifth and sixth cervical nerves. Three months after the onset there was pronounced atrophy of the affected muscles. Complete recovery followed eight months of treatment with vitamin B therapy and physical therapy.

BERLIN, Chicago [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MECHANISM OF ACTION AND THERAPEUTIC USE OF DIURETICS. ROBERT F. PITTS and OTTO W. SARTORIUS, J. Pharmacol. & Exper. Therap. **98**:161 (April) 1950.

There are 52 pages of text and 504 references in this most interesting review of the physiological and pharmacological actions and therapeutic uses of diuretics. It is too long for abstraction in this journal but the authors' conclusions (on pages 212 and 213 in the article) are so practical for the pediatrician that they are here given in toto.

"In the edematous patient the quantities of salt and water absorbed by the renal tubules are excessive relative to those delivered into the tubules in the glomerular filtrate. In consequence, fluid and electrolyte are retained and diverted peripherally to expand the interstitial reservoirs of the body. The major action of the 5 classes of diuretics discussed above is depression of the renal tubular absorption of salt and water. Use of these agents to reverse the abnormal processes which lead to the accumulation of edema therefore constitutes rational therapy.

"All diuretics must be employed with care in patients with severely reduced renal function, and especially in those with absolute renal insufficiency, because the capacity of the diseased kidney to compensate for the insult of injudicious therapy is reduced. They must not be used at all in the presence of anuria, since each, if accumulated in the body in excess, is toxic. This applies no less to large quantities of water which may produce fatal dilution than to more obviously toxic substances such as potassium and mercury which may cause cardiac arrest or tissue damage.

"Despite the necessity for caution, diuretics should be used for the relief of edema, not as a last resort when massive accumulation of fluid itself jeopardizes life. Treatment should be individualized, not administered by rule of thumb. In each instance one should employ the most benign drug capable of causing the desired fluid loss, in the minimum effective dose and at such intervals as are necessary to avoid marked fluctuations in weight.

"There is reason to believe that more effective and safer diuretic agents may be developed in the future. This optimism is based on two facts. First, the most effective agents available at present, namely, the organic mercurial compounds, when administered in maximal and just sublethal doses block the reabsorption of only 20 per cent of the salt and water normally returned from the glomerular filtrate to the blood stream. If more were known of the chemical and physical processes involved in tubular transport, the remaining 80 per cent might be made vulnerable to therapeutic attack. Not that one would dare block reabsorption completely, but an agent which could accomplish this end would be a highly effective diuretic when administered in small quantities. Second, no less than four factors are now recognized as being causally related to overabsorption of water and salt by the renal tubules, namely, reduced glomerular filtration rate, elevated renal venous pressure, and excessive stimulation by adrenal cortical and posterior pituitary antidiuretic hormones. It is possible that effective means might be found to raise filtration rate, reduce venous pressure, and inhibit either the secretion or the renal target action of the above mentioned hormones. Such therapy would constitute a truly physiological means of combating edema."

PILCHER, Cleveland.

CLINICAL OBSERVATIONS ON TERRAMYCIN IN PEDIATRIC INFECTIONS. T. G. POTTERFIELD and G. A. STARKWEATHER, J. Philadelphia Gen. Hosp. **2**:6 (Jan.) 1951.

Potterfield and Starkweather studied the results of terramycin therapy in 62 children, of which number six had otitis media, four tonsillitis, one sinusitis, and one laryngotracheobronchitis. It was found that terramycin is an effective therapeutic agent in respiratory infections due to Diplococcus pneumoniae, Micrococcus pyogenes (Staphylococcus) variety aureus, Hemophilus influenzae, and beta hemolytic streptococci. All the patients with otitis media had fever on admission to the hospital (temperature between 102 and 105 F.). Within 24 to 48 hours after terramycin therapy was started, their temperature returned to normal. One child required a myringotomy. The four patients with tonsillitis became afebrile in 48 hours. Cultures grown from material from the throat revealed hemolytic Streptococcus in three and beta hemolytic Streptococcus in one. A 7-month-old patient had laryngotracheobronchitis but became afebrile in 48 hours after terramycin therapy was begun. The general clinical picture of this child improved satisfactorily after the third day. One 6-year-old patient with maxillary and ethmoid sinusitis showed marked clinical improvement 24 hours after terramycin therapy was started and became afebrile in 48 hours. The other children in this series had pneumonia. In this group of 62 children no toxic manifestations were observed, and the authors felt that terramycin was effective in the treatment of the common bacterial respiratory tract infections of children.

GORDON, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

TETANUS RESULTING FROM A FOREIGN BODY IN THE NOSE. MATTHEW LINKER, IRA M. ROSENTHAL, and JOSEPH GOLOMB, New York J. Med. **50**:1620 (July) 1950.

The authors, who report this case from Fordham Hospital, New York City, say that they have been unable to find in the literature any previously recorded instance of tetanus from nasal foreign body. On Aug. 12, 1948, a 17-month-old Negro child was admitted with a purulent profuse nasal discharge, dysphagia, anorexia, and weakness. Nothing in the history explained the symptoms, and there was no evidence of wound infection anywhere. His temperature was around 100 F.; he had tachycardia. Frequent irrigations brought a paper match stick out of one nostril. Culture showed Escherichia coli, Staphylococcus aureus, and Clostridium tetani from the match stick. Streptomycin and penicillin had been given before the tetanus was diagnosed. Thereafter, large doses of tetanus antitoxin were administered. Improvement, however, was slight, and death occurred on Aug. 17, the fifth day after admission. Autopsy was not permitted.

The importance of routine immunization of children against tetanus is stressed, and the authors say, "It is possible that with earlier diagnosis tracheotomy, tribromoethanol, curare or mephenesin might have contributed to a more satisfactory result in this case."

VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

PENICILLIN RESISTANCE OF NONHEMOLYTIC STREPTOCOCCI FROM RHEUMATIC CHILDREN RECEIVING PROPHYLACTIC PENICILLIN. ELSA KRUMWIEDE, Pediatrics **4**:634 (Nov.) 1949.

The nonhemolytic streptococci in the throats of children receiving penicillin orally for prophylaxis tend to be more resistant than those isolated from children who are not receiving penicillin. Children who are not receiving penicillin carry some strains which are as resistant as those carried by children receiving penicillin prophylaxis.

The higher resistance of the nonhemolytic streptococci isolated from children receiving penicillin prophylaxis appears, in most instances, to be due to the selection of resistant, and the elimination of more sensitive, strains.

Although the penicillin resistance of nonhemolytic streptococci isolated from the throats of children receiving prophylactic penicillin is increased, the resistance is not as great as that reported for some strains of nonhemolytic streptococci isolated from patients who were successfully treated for subacute bacterial endocarditis.

FROM THE AUTHOR'S SUMMARY.

UNUSUAL SYNDROME ASSOCIATED WITH CANDIDA ALBICANS INFECTION. KATHARINE H. BAIRD, Pediatrics **4**:730 (Dec.) 1949.

A syndrome associated with Candida albicans (Monilia) infection and first described by Schultz includes a focus of infection in the mouth and the gastrointestinal tract, plus alopecia, dwarfing, paronychia, and eruptions of skin lesions involving the face, perineum, and localized symmetric lesions on the extremities. The patient with this syndrome responded to oral thymol therapy (0.192 gm. three times daily) and has continued to make good progress, although he still shows evidence of persisting C. albicans infection. FROM THE AUTHOR'S SUMMARY.

CHLOROMYCETIN AS TREATMENT OF PARATYPHOID B SALMONELLOSIS IN INFANCY AND EARLY CHILDHOOD. E. PLANSON, Presse méd. **57**:1083 (Nov. 26) 1949.

Encouraged by the favorable results of treatment of typhoid with chloramphenicol (chloromycetin®) given orally, Planson tried this antibiotic in the treatment of salmonellosis. The dosage given was 0.25 gm. four times during the first day, then 0.25 gm. three times daily for three or four days. Results were prompt and favorable. DAFFINEE, Melrose, Mass.

TWO CASES OF TULAREMIA TREATED WITH CHLOROMYCETIN. F. KARCHER, Presse méd. **58**:96 (Feb. 4) 1950.

A man and his 10-year-old son were stricken simultaneously with tularemia as a result of tasting rabbit meat before it was cooked. The members of the family who ate the meat only after it was cooked were not affected. Chloramphenicol (chloromycetin®) was given empirically for three days before the diagnosis was made, with excellent results. Four days after treatment was stopped, recrudescence occurred, with the same symptoms as the original attack. Chloramphenicol was again given, this time for six days, and recovery was complete.

DAFFINEE, Melrose, Mass.

CHLOROMYCETIN IN EPIDEMIC TYPHUS. E. BENHAMOU, F. DESTAING, and A. SORREL, Presse méd. **58**:317 (March 25) 1950.

The authors compare the results of treatment of epidemic typhus with chloramphenicol (chloromycetin®) with those obtained with aureomycin. Both antibiotics were efficacious, producing recovery in three to five days. Aureomycin caused a more rapid drop of fever. Chloramphenicol is of value also in the treatment of typhoid, and it is therefore to be preferred when the diagnosis is in doubt. In areas where both diseases are to be found, difficulty in diagnosis arises because of the appearance or increase in typhoid coagglutins in the presence of typhus. At the same time, chloramphenicol does not prevent the development of the Weil-Felix reaction, and the diagnosis of typhus becomes evident within a few days.

DAFFINEE, Melrose, Mass.

MYELOGRAM IN DYSENTERY IN CHILDHOOD. G. CADEDDU, Ann. ital. pediat. **2**:468 (Dec.) 1949.

Cadeddu has studied the myelograms of 30 children affected with the dysentery form of enteritis. He did not observe remarkable or specific modifications. He found a significant increase of the eosinophile cells in a great number of subjects and an accelerated production of all granuloblastic cells; but although that represents a manifestation of a strongly accentuated reaction of the bone marrow, produced by the infectious form, it is not possible to consider that modification as a characteristic. FROM THE AUTHOR'S SUMMARY.

TREATMENT OF THRUSH WITH GENTIAN VIOLET. A. VERGA, Minerva pediat. **3**:159 (March) 1951.

Gentian violet seems to clear up thrush as quickly as does sodium perborate. Crystal violet similarly will relieve the condition, but in the author's experience several of the children receiving this dye showed constitutional reactions. HIGGINS, Boston.

SEROLOGICAL STUDIES WITH CHILDREN HAVING AN INFLUENZAL INFECTION. S. VIRIDIS and A. FOIS, Minerva pediat. **3**:177 (March) 1951.

In an epidemic of influenza in Milan in 1949, the sera of 57 affected children were tested for influenza antibodies by inhibition of hemoagglutinins (Hirst's reaction) and by complement fixation.

HIGGINS, Boston.

EFFECT OF GAMMA GLOBULIN TREATMENT ON THE AMOUNT OF COMPLEMENT IN THE SERA OF CHILDREN. L. BASSI and ANGELA M. FERUTTA, Minerva pediat. **3**:182 (March) 1951.

Forty-eight children—some healthy and some sick—were given injections of gamma globulin. The amount of complement in the sera of 33 children was unchanged after the injection; it was increased in the sera of 6, and diminished in the sera of 9. The efficacy of gamma globulin is apparently not due to any action on the amount of blood complement.

HIGGINS, Boston.

TYPHOID AND SALMONELLA INFECTIONS IN INFANTS. G. TACCONE, Pediatria **58**:310 (May) 1950.

All Salmonella organisms should be regarded as pathogenic, regardless of their human or animal origin. For clinical interpretation and treatment, however, the patients with Salmonella infections should be divided into groups according to the symptoms and course of the disease.

HIGGINS, Boston.

COXSACKIE VIRUS INFECTION. E. ARNE DAHLSTROM, Acta pædiat. **40**:235 (May) 1951.

An account is given of two cases of Coxsackie virus infection in children. The patients recovered without specific therapy and were discharged from the hospital entirely free of symptoms.

FROM THE AUTHOR'S SUMMARY.

BLEEDING OF THE NOSE AS A SIGN OF RHEUMATIC FEVER. J. L. KEYZER, Maandschr. kindergeneesk. **17**:254, 1949.

Attention is drawn to the fact that heavy epistaxis proved to be the first sign of relapsing rheumatic fever in five children.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

COCCIDIOIDIN SKIN TESTING DURING PREGNANCY AND IN INFANTS AND CHILDREN. ROBERT COHEN and ROBERT BURNIP, California Med. **72**:31 (Jan.) 1950.

Results of a study of 220 newborn infants in an endemic area indicate coccidioidal infection is not transmitted congenitally. Skin testing of 595 infants and children disclosed that coccidioidal infection may be acquired at a very early age—as early as one month. The children tested were divided into various age groups, and the incidence of infection increased gradually from the lowest age group to the highest.

PRYOR, Redwood City, Calif.

TUBERCULOUS OTITIS AND MENINGITIS. D. I. ARBUSE and E. LEVENSON, J. Nerv. & Ment. Dis. **113**:165 (Feb.) 1951.

Of a series of 42 patients with tuberculous meningitis, two had associated tuberculous otitis media. One, a man aged 46, had chronic otologic disease of three years' duration, and one year prior to his admission the aural discharge was found to contain tubercle bacilli. He died of lymphocytic meningitis, from which tubercle bacilli were not cultured. The second patient, a girl aged 18 years, had had a draining ear for 10 years, from which tubercle bacilli were ultimately cultured. Lymphocytic meningitis developed, and pellicle and Levinson tests gave positive results. She showed improvement for one year while receiving streptomycin therapy.

BERLIN, Chicago [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EFFECT OF STREPTOMYCIN ON TUBERCULOUS MENINGITIS. A. LEVINSON, J. A. LUHAN, W. P. MAVRELIS, and H. HERZON, J. Neuropath. & Exper. Neurol. **9**:406 (Oct.) 1950.

In this investigation the authors studied the pathologic picture in tuberculous meningitis and the associated generalized miliary tuberculosis in 26 cases in which streptomycin was therapeutically employed.

Thirty-eight infants and children were treated. Seven of the patients made apparent recoveries, with complicating hemiparesis in one and deafness in two. The longest survival period to date is two and one-half years, the patient being still alive.

Of the 38 cases in the series, necropsy was performed in 23; with the addition of three others (two of adults), these form the basis of the present study. Treatment consisted in intramuscular administration of streptomycin, usually 0.2 gm. every three hours. No intrathecal therapy was given, except to the first patient, who received nine intraspinal injections, and to two patients who had received previous treatment at other hospitals, including 23 and 24 intrathecal injections, respectively. Treatment was continued for at least 90 days unless the patient did not live that long; in addition, if a relapse occurred, further treatment with streptomycin was given, until death.

This report is an analysis of the pathologic findings in 16 cases in which life was prolonged a minimum of 35 days, with a study of 10 additional cases in which death occurred within 30 days of onset in order that the early effects of streptomycin treatment might be determined.

After prolonged therapy (a minimum of 90 days) changes associated with advanced healing were observed in the miliary lesions in the viscera and in the exudate of the meninges. Notwithstanding, there were usually present caseous or incompletely healed miliary foci and similar unhealed foci in the meninges.

The mechanism of healing of tuberculous lesions in the meninges and viscera was found to be a process of diminishing cellularity and progressive fibroplasia. Frequent features of the brain in these cases of streptomycin-treated meningitis were (1) ischemic or necrotic softenings in the rostral basal ganglia on the side opposite the hemiparesis (31%); (2) a greater incidence of high degrees of internal hydrocephalus than had been observed in cases of the untreated disease; (3) selective involvement of the stem of the Sylvian fissure with a thick granulomatous exudate, within which occurred endarteritis of branches of the middle cerebral artery supplying the basal ganglia, the cause of the ischemic softenings.

The mechanism of healing of the exudate, by the formation of a thick fibrous scar at the base of the brain, associated with endarteritis of arteries traversing the exudate, stands as an obstacle to uncomplicated recovery in streptomycin-treated tuberculous meningitis.

The most important clinical problem in the treatment of tuberculous meningitis is that of "relapse." Relapse in cases of streptomycin-treated tuberculous meningitis is here explained as resulting usually from a repeated miliary dissemination to the meninges from unhealed caseous foci in the body and occasionally from local breakdown of minute caseous foci within the meninges.

Levinson and his co-workers believe that intrathecal therapy is generally not necessary in cases of tuberculous meninges. They feel that the present pathologic report adequately demonstrates that healing can be effected without resort to intrathecal therapy. The only two patients in this series receiving intensive intrathecal therapy (given at other hospitals) arrived in a moribund state.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EXPERIMENTAL CONGENITAL TOXOPLASMOSIS: IV. GENITAL AND SECONDARY LESIONS IN THE MOUSE INFECTED WITH TOXOPLASMA BY THE VAGINAL ROUTE. D. COWEN and A. WOLF, J. Neuropath. & Exper. Neurol. **10**:1 (Jan.) 1951.

Cowen and Wolf studied the character and spread of infection of the genital tract with Toxoplasma in the adult mouse as revealed by postmortem examination of its tissues. The pathologic observations are based on the postmortem examination of 302 mice infected by the vaginal route. For the entire series the duration of life after the first exposure to Toxoplasma varied from 3 days to 11 weeks, but the majority of the animals were examined two to four weeks after the initial inoculation.

It was found that primary inflammatory lesions developed in the vaginal wall of mice three to five days after the introduction of Toxoplasma into the vagina. After a further interval of six to eight days, specific focal inflammatory and necrotizing lesions appeared in distant organs, most constantly the central nervous system, lungs, and heart. The secondary lesions had the pathologic characteristics of a blood-disseminated infection and resembled those seen in animals inoculated by other peripheral routes.

The lesions in the nervous system consisted of small foci of inflammation, associated with varying degrees of degeneration of parenchymal elements. Lymphocytes, large mononuclear cells, and polymorphonuclear leucocytes constituted the majority of the cells in the exudate, with an increase of the last-named type in the more acute lesions and in the presence of necrosis. In animals which survived the first few weeks of infection there was a distinct tendency for the pathologic process to subside in intensity and to become histologically "chronic." In the nervous system, calcification of healed lesions was occasionally seen. Parasites were more numerous in the early lesions. They progressively decreased in number as the acute stages were passed.

Cowen and Wolf found no tendency for the infection to ascend directly from the vagina into the upper part of the genital tract. The pathologic observations suggested that the parasitemia and generalized toxoplasmosis developed during the earlier phases of the vaginitis and that the vagina did not constitute a focus of chronic infection from which toxoplasmas might continue to be disseminated or expelled. Parasites were present in the early vaginal lesions but were not seen in histologic sections after the 19th day of the disease. Histologically demonstrable toxoplasmas persisted in the brain as "cysts" for many weeks without progression or reactivation of the infection in this organ or elsewhere.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MIXED INFECTION OF HEMOLYTIC STREPTOCOCCI IN CASES OF PRIMARY TUBERCULOSIS IN CHILDREN. SVEN-IVAR ROLLOF, Pediatrics **4**:412 (Oct.) 1949.

A survey of the literature on the occurrence of hemolytic streptococci and antistreptolysin in healthy subjects and on recent investigations of mixed infections in tuberculosis is presented.

In 190 cases of primary tuberculosis in children aged 1 to 15 years, Streptococcus hemolyticus was found in the pharynx, and among 130 such cases antistreptolysin titers over 200 were found to be considerably more frequent than they were in healthy children or other healthy subjects.

Cases of primary tuberculosis in which the symptom first manifested was an eruption of erythema nodosum formed a special group, with a high frequency of streptococcic infection.

FROM THE AUTHOR'S SUMMARY.

THE SWEDISH BCG EXPEDITION IN GERMANY. HERBERT NATHHORST, Pediatrics **4**:430 (Oct.) 1949.

The Swedish BCG action in Germany has progressed according to schedule. Great interest has been shown by the German medical profession and by the population. This is best shown by the fact that the number of persons requesting vaccination is steadily increasing, and also by the fact that such a large number of German physicians have been instructed during this period that it is now merely a question of time before the Swedish personnel will not be needed. The BCG vaccination has shown also that when a country is threatened by tuberculosis, in a fairly short time interest can be awakened in the BCG vaccination, among the physicians as well as among the general public, so that the vaccination program will subsequently be continued.

FROM THE AUTHOR'S SUMMARY.

BCG VACCINATION IN SWEDEN. JOHN LUNDQUIST, Pediatrics **4**:430 (Oct.) 1949.

It may be said without exaggeration that BCG vaccination is received favorably among the Swedish population; there has been no reaction registered against it similar to that resistance which occasionally is asserted against smallpox vaccination.

FROM THE AUTHOR'S SUMMARY.

SKIN REACTIONS TO TOXOPLASMIC ANTIGEN IN PEOPLE OF DIFFERENT AGES WITHOUT KNOWN HISTORY OF INFECTION. HARRY A. FELDMAN and ALBERT B. SABIN, Pediatrics **4**:798 (Dec.) 1949.

One hundred forty-two residents of Cincinnati, aged 3 months to 81 years, were surveyed for reaction to intracutaneous toxoplasmic antigen prepared from infected chorioallantoic membranes of chicken eggs. The skin test antigen is also present in mouse peritoneal exudate freed of Toxoplasma by centrifugation, and its concentration appears to be proportional to that of complement-fixing antigen. Positive reactions, consisting of red, indurated, swollen, tender, and itching lesions 60 by 50 mm. in size to 10 by 10 mm. (the latter being relatively rare), reach their maximum in 30 to 48 hours. The incidence of positive reactions among at least 20 persons in each age group listed was 0 to 4 years, 0; 5 to 10 years, 5%; 10 to 19 years, 14%; 20 to 29 years, 20%; 30 to 39 years, 50%; 40 to 49 years, 65%; 50 to 81 years, 65%. A positive skin reaction was invariably associated with demonstrable toxoplasmic antibody in the serum.

Toxoplasmic antibody in varying titers was also found in the serum of 7 to 18 persons (39%) with negative skin reactions. Further evidence in favor of the high incidence of toxoplasmic antibody among the "normal" adult population was obtained when a 15 to 20-times concentrated, commercial preparation of gamma globulin prepared from the plasma of more than 20,000 American adults was found to contain toxoplasmic antibody in a titer of 1:256, as determined by the dye test. Since no agent having an antigen in common with toxoplasma and capable of giving rise to antibodies for this protozoon parasite has been found thus far, one must consider the possibility that inapparent infection with toxoplasma may be widespread, although it is rather curious that the incidence of antibodies (and presumably infection) should rise so sharply after the 20th year of life. The toxoplasmic skin test is not useful for diagnosis because a strongly positive reaction bears no relationship to the titer of antibody and a negative reaction is encountered too often in the presence of antibody.

FROM THE AUTHORS' SUMMARY.

STAGES OF TUBERCULOUS INFECTION. P. F. ARMAND-DELILLE, Presse méd. **58**:45 (Jan. 21) 1950.

The author wishes to correct Ranke's fundamental ideas on the development of tuberculous lesions. His experiments show that there are three steps in the development of tuberculosis: (1) inoculation, with local reaction; this tends to heal, but sensitizes the whole body; (2) extension through lymphatics or blood vessels, with bacteremia and some further allergic reaction; and (3) localizing lesions appearing some time after the initial infection. Antibiotics, therefore, should be used in the early second stage and in the acute phases of the third stage.

DAFFINEE, Melrose, Mass.

LESSONS FROM TREATMENT IN 128 CASES OF TUBERCULOUS MENINGITIS DURING THE THREE YEARS (1947, 1948, 1949) THAT THE STREPTOMYCIN CENTER OF BOLOGNA HAS BEEN FUNCTIONING. L. MARTONI and P. NICOLAJ, Clin. Pediat. **32**:393 (Aug.) 1950.

Streptomycin has been used to treat 128 patients with tuberculous meningitis during the three years 1947 to 1949; of these, 72 have been cured and 56 have died. Excluding those patients in whom death occurred during the first five days of treatment, and those transferred from other hospitals in very serious condition, 72 of 101 patients recovered. When the treatment was begun during the first five days of meningeal symptoms, the mortality rate was 19%, as compared with 67% when treatment was started later.

The mortality rate for patients from birth to 2 years of age was 52%, from 3 to 6 years 46%, from 7 to 12 years 34%, from 13 to 20 years 33%, and over 21 years 50%. Patients with hilus tuberculosis or miliary tuberculosis had a better prognosis (24% mortality) than those with pulmonary infiltration (41% mortality), or those with miliary tuberculosis and pulmonary infiltration (67% mortality). Only six of the patients showed relapses after a cure seemed established; these patients responded well to further streptomycin therapy. Many of the patients are in good condition two years after the completion of treatment.

The daily dose of streptomycin per kilogram of body weight was 2 to 3 mg. intrathecally and 20 to 30 mg. intramuscularly. Supplementary medication consisted of vitamins A, B, C, and

D_5, and often of paraaminosalicylic acid. The average duration of treatment for the patients who recovered was 257 days. The clinical course of the treated patients, especially the neurological and ocular signs, and the laboratory findings are described. Two cases of streptomycin allergy were seen.

HIGGINS, Boston.

BLOOD IRON LEVEL IN CHILDHOOD TUBERCULOSIS. M. LATO, Clin. pediat. **32**:457 (Sept.) 1950.

Observation of 10 children with tuberculosis revealed slight hypochromic anemia, normal number of reticulocytes, increased sedimentation rate, and low blood iron content. The sedimentation rate decreased as the patient's condition improved, but the blood iron content remained unchanged.

HIGGINS, Boston.

PRELIMINARY REPORT ON THERAPEUTIC RESULTS FROM USE OF SODIUM PARAAMINOSALICYLATE INTRASPINALLY IN TUBERCULOUS MENINGITIS IN INFANTS. E. COSSANDI and L. MAGGIORA, Lattante **21**:507 (Aug.) 1950.

Of five infants treated with streptomycin and sodium paraaminosalicylate intrathecally, three were cured and two died. Each of the infants who recovered received 95 to 137 spinal treatments; in 25 to 50% of these patients streptomycin (50 mg.) as injected, and in the others sodium paraaminosalicylate (20 mg. per kilogram of body weight). The intrathecal treatments were supplemented with streptomycin given intramuscularly and paraaminosalicylate acid orally. There were no untoward reactions following the sodium paraaminosalicylate injections. The authors were favorably impressed with the effects of the therapeutic synergy.

HIGGINS, Boston.

LIMITS OF EFFICACY OF PARAAMINOSALICYLIC ACID (PAS) IN PULMONARY TUBERCULOSIS OF CHILDREN AND INDICATIONS FOR COMBINED PARAAMINOSALICYLIC ACID (PAS) AND STREPTOMYCIN THERAPY. R. BULGARELLI, Minerva pediat. **2**:297 (July) 1950.

One hundred eighty-five children with tuberculosis, treated at the Pediatric Clinic of the University of Genoa, are listed as having received paraaminosalicylic acid, either alone or in combination with streptomycin. The author's clinical experience permits him to draw the following conclusions: 1. Paraaminosalicylic acid has a definite therapeutic value in tuberculosis; however, it is definitely less than that of streptomycin. 2. The exclusive use of paraaminosalicylic acid in the treatment of tuberculosis of a serious nature is not advisable. 3. Intrathecal injections of paraaminosalicylic acid are not well tolerated over a long time, and, further, in the doses that can be given do not seem to exercise any important beneficial effect on the tuberculous meningitic process.

HIGGINS, Boston.

EVOLUTION OF TUBERCULOUS CYCLE IN A PATIENT WITH A PRIMARY TUBERCULOUS FOCUS. S. APRILE and A. BLASI, Pediatria **58**:550 (July) 1950.

The phases of tuberculosis are pointed out in the case of a boy of 13 years who died 13 months after the onset of symptoms. These phases are (1) appearance of the primary lesion, (2) development of allergy, (3) adenopathy, caseation, and ulceration, and (4) miliary involvement and meningitis.

HIGGINS, Boston.

CASE OF CONGENITAL TOXOPLASMOSIS, PROVED CLINICALLY, SEROLOGICALLY, AND PARASITOLOGICALLY, WITH NO ENDOCRANIAL CALCIFICATION AND NO GROSS PATHOLOGICAL CHANGES IN THE BRAIN. L. MORO and U. GIURANNA, Pediatria **58**:569 (July) 1950.

The causation in this case is believed traceable to a bite from a seemingly healthy dog received by the mother early in the pregnancy. Dogs have ben recognized as carriers of the Toxoplasma and may transmit the disease by bites or by licking an open cutaneous lesion. The child was abnormal from birth; she was spastic, especially on the right side, and was mentally retarded. The skull roentgenogram revealed no areas of localized calcification. Ophthalmological

examination revealed a degenerative chorioretinitis, with small areas of depigmentation in the retina. Both the mother and the child yielded positive reactions for Toxoplasma by the Sabin-Feldman serum test. The child died at the age of 22 months during an attack of measles-pneumonia. At postmortem examination the brain showed no gross pathologic changes; the Toxoplasma parasite was found in sections of the lung and spleen.

HIGGINS, Boston.

PRIMARY CUTANEOUS TUBERCULOSIS COMPLEX. JULIO MOWBRAY BARBERAN, Acta pediat. españ. **33**:1077 (Sept.) 1950.

The author reports a case of primary tuberculous lesion in the skin of a girl of 3½ years who was followed over a period of three years. There was a very definite family history of tuberculosis. The father had once had a hemorrhage but now was considered to have arrested disease. An uncle had died of tuberculosis. The mother was healthy, but one child had died of tuberculosis at the age of 2 years, and another had definite tuberculosis and after treatment remained at home a semi-invalid with coxalgia.

The child had never had any serious illness until this lesion appeared, at the right side of the nose in the sulcus. The tuberculin test and a roentgenogram of the chest showed nothing abnormal. The lesion was not affected by local treatment. Wassermann and Kahn reactions were negative. The dark-field examination and the test for leishmaniasis also showed nothing abnormal. Consent for a biopsy could not be obtained.

The lesion was round and between 0.5 and 1 cm. in diameter; the edge was elevated, the center grayish and ulcerated in appearance, with a small amount of secretion. The surrounding skin was red, and maxillary lymph nodes were enlarged on the same side.

The child began receiving large amounts of vitamin D, calcium, and vitamin C and was sent to the country to the place where her brother had been treated. After a period of one and one-half months, she had gained 980 gm., the lesion was healing, and a definite adenopathy was present, with reddening of the skin and fluctuation in some nodes. There was a new invasion of the submental nodes and eventually three fistulas developed. The parents objected to surgery or the use of guinea-pig inoculation. The second tuberculin test, done after two months, was strongly positive for bacilli.

Radiotherapy and general supportive measures were the only treatment, and three years after the initial lesion the lungs are normal with no Ghon tubercles present. The fistulas healed with only the usual scars.

The author believes that although all the requirements formulated by Krantz could not be fulfilled, the child had a primary tubercle of the skin, possibly contracted from a kiss from her brother.

ALLEN, Santa Fe, N. Mex.

Diseases of Blood, Heart and Blood Vessels, and Spleen

COR TRILOCULARE BIATRIATUM: AN ANALYSIS OF THE CLINICAL AND PATHOLOGIC FEATURES OF NINE CASES. H. M. ROGERS and J. E. EDWARDS, Am. Heart J. **41**:299 (Feb.) 1951.

Nine cases of cor triloculare biatriatum, which represent all cases of this anomaly in the collection of pathologic specimens in the Mayo Clinic, are reviewed pathologically and clinically.

In eight patients there was associated transposition of the great vessels. In six of these the outflow tract of the common ventricle was so divided as to create a narrow tract leading to the aorta. The pulmonary trunk was wide. In the other two patients a subpulmonary fibrous collar created a moderate degree of subpulmonary stenosis.

The ninth patient (Case 6) was unusual in that the great vessels were not transposed.

Coarctation of the aorta was associated with cor triloculare biatriatum in two patients. In one of these tubular hypoplasia of the aortic arch between the left common carotid and left subclavian arteries also was present. In still another patient this aortic abnormality existed but without associated coarctation.

Six of the nine patients were male, and three were female. The age at death varied from 3 weeks to 8 years. Records of physical examination were available for seven patients, and each showed the presence of a precordial systolic murmur. At times, this was associated with

a precordial thrill. Cyanosis varied in degree. In one instance it was not recognized until the patient was 7 months of age. In several instances cyanosis was mild and became intensified only before the patient's death. Mongolism was associated with cor triloculare biatriatum in one patient, and isolated dextrocardia occurred in one patient. Electrocardiographic examination revealed right axis deviation in two patients and left axis deviation in two.

FROM THE AUTHORS' SUMMARY.

CONGENITAL VENTRICULAR SEPTAL DEFECT WITH ACQUIRED COMPLETE HEART BLOCK. H. M. ROGERS and C. C. RUDOLPH, Am. Heart J. **41**:770 (May) 1951.

A case of congenital ventricular septal defect and acquired complete heart block is presented. When first examined, at 2½ years of age, the patient had normal atrioventricular conduction. At the age of 4 years persistent complete heart block developed. This was accompanied with Adams-Stokes attacks. Death occurred during an attack of Adams-Stokes syncope. The association of acquired complete heart block with congenital cardiac disease is very uncommon.

FROM THE AUTHORS' SUMMARY.

ATYPICAL PATENT DUCTUS ARTERIOSUS WITH ABSENCE OF THE USUAL AORTIC-PULMONARY PRESSURE GRADIENT AND OF THE CHARACTERISTIC MURMUR. G. S. MYERS, J. G. SCANNELL, S. M. WYMAN, E. G. DIMOND, and J. W. HURST, Am. Heart J. **41**:819 (June) 1951.

The authors report two cases of patent ductus arteriosus in children proved by operation in which the characteristic machinery murmur was not heard. Catheterization of the heart revealed markedly elevated diastolic pressures in the pulmonary circuit, approaching that of the systemic diastolic pressure. The high diastolic pressure would suggest minimal blood flow through the ductus during diastole, and thus the absence of the typical diastolic phase of the murmur would be accounted for.

GIBSON, Chicago.

SPLENIC CYSTS. H. T. TAMAKI, Arch. Path. **46**:550 (Dec.) 1948.

Splenic cysts are rare. The author discusses the nonparasitic, or false, cysts, which are of the greatest clinical importance. He reports a case in a 15-year-old white boy who was found to have an abdominal mass in the left upper abdomen on routine examination. Four years previously the patient had a fall followed by slight enlargement of the abdomen just beneath the margin of the left rib. The peritoneal cavity was unsuccessfully tapped for blood, with the possibility of a ruptured spleen in mind. The mass had remained constant in size but gradually and rapidly increased in size three months before the above examination. The patient complained only of a "pulling sensation" in the affected area. Examination disclosed a resilient mass, moving slightly with respiration, extending 14 cm. below the left costal margin. Urinalysis revealed a trace of albumin and occasional leucocytes. The hemoglobin was 88%, red blood cells 4,530,000, white blood cells 6,300 with 71% polymorphonuclear leucocytes, 28% lymphocytes, and 1% eosinophiles. Roentgenograms showed a curvilinear shadow of calcification transversely across the abdominal mass. The patient was operated upon, and a hemorrhagic cyst of the spleen was removed. Secondary splenic cysts vary in size. One-fourth of the cases have a history of trauma, and nearly 80% are of the hemorrhagic type. There is only one method of choice for treatment of splenic cysts—that of splenectomy. Mortality rates reported are approximately 4%. Other methods have been tried, such as marsupialization, puncture, coagulation, and extirpation, but the results from these procedures have been generally unsatisfactory.

HAW CHAN, San Francisco.

CONGENITAL RHABDOMYOMATOSIS OF THE HEART: REPORT OF A CASE WITH AUTOPSY. AMBROSE J. HERTZOG, Arch. Path. **47**:191 (Feb.) 1949.

The case of a 2-month-old white infant dying of heart failure is reported. At autopsy diffuse rhabdomyomatosis of the heart was found. The author interprets the tumors as hamartomas.

HAW CHAN, San Francisco.

RIGHT AORTIC ARCH WITH A VASCULAR RING CONSTRICTING ESOPHAGUS AND TRACHEA. BELA HALPERT, WILLIAM T. SNODDY, KENNETH E. BOHAN, and CHARLES L. FREEDE, Arch. Path. **47**:429 (May) 1949.

Autopsy findings of a right aortic arch with a vascular ring are reported in two infant girls. For the first patient, 7 months old, the diagnosis of congenital heart disease was made at the age of 7 weeks, because of the findings of an enlarged cardiac shadow and right ventricular hypertrophy. After this there were repeated episodes of respiratory difficulties associated with spells of cyanosis. Two days before her last admission she was noted to choke with feedings. The second patient, 5 months old, was noted at the age of 10 weeks to have wheezing respirations and a nonproductive cough. Feeding of 2 oz. (60 ml.) of formula caused regurgitation and at times initiated attacks of crying, cyanosis, and perspiration. Sleeping in an upright position seemed to alleviate difficulties. In the first case the diagnosis of a vascular ring constricting the esophagus was not made until autopsy. In the second case the clinical diagnosis was made at the last admission, and an attempt to relieve surgically the tension on the trachea and esophagus was successful. However, the patient's general condition was very poor, and she died eight hours after the operation. In the two cases findings were similar as regards the anomaly of the aorta. The ascending portion of the aorta arched over the right main bronchus and passed down to the right of the esophagus. From the arch arose, in order, left common carotid, right common carotid, and right subclavian arteries. The left subclavian artery arose in both cases from a medial diverticulum of the aorta (remains of the fourth arch). The left subclavian then continued into an obliterated ductus arteriosus, which connected with the left branch of the pulmonary artery. The arterial ring thus formed encircled the esophagus and trachea.

HAW CHAN, San Francisco.

PORPHYRIN FORMATION IN HEMOGLOBIN METABOLISM IN CONGENITAL PORPHYRIA. I. M. LONDON, R. WEST, D. SHEMIN, and D. RITTENBERG, J. Biol. Chem. **184**:365, 1950.

The studies reported here were conducted on a patient with congenital porphyria who excretes large amounts of uroporphyrin I and coproporphyrin I. They were directed to the following problems: (*a*) to determine whether glycine (amino-acetic acid) is specifically utilized in the biologic synthesis of porphyrins related to the etioporphyrin-I configuration as it is utilized in the synthesis of protoporphyrin, which is related to the etioporphyrin-III configuration; (*b*) to measure the rates of formation (and degradation) of uroporphyrin I and coproporphyrin I; (*c*) to investigate the life span and pattern of destruction of the erythrocyte and the origins of bile pigment in this disease. Glycine is specifically utilized in the biologic synthesis of porphyrins related to the etioporphyrin-I configuration. The rates of formation and degradation of uroporphyrin I and of coproporphyrin I in a subject with congenital porphyria are found to be rapid. A normal average life span of the erythrocyte of about 120 days was observed in this subject with congenital porphyria. A large part, at least 31%, of the stercobilin in this subject is derived from sources other than the hemoglobin of mature, circulating erythrocytes. The nature of these possible sources is discussed.

PAGE, Cleveland [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

INFANT METHEMOGLOBINEMIA IN MINNESOTA DUE TO NITRATES IN WELL WATER. A. B ROSENFIELD, and ROBERTA HUSTON, Minnesota Med. **33**:787 (Aug.) 1950.

A study of 146 cases in infants of methemoglobinemia due to nitrates in farm well water supplies in Minnesota is reported. Formulas incorporating large amounts of water are most dangerous. Nitrates occur more frequently in shallow wells than in deep wells. The nitrate concentration of the well water remains fairly constant, and significant seasonal variations do not occur. It is generally accepted that water with over 10 ppm. of nitrate nitrogen should be considered dangerous because of the resultant concentration of the nitrates reached by boiling the water. In this study all of the cases of methemoglobinemia in which sufficient data were obtained occurred from using water with more than 30 ppm.

STOESSER, Minneapolis.

CARDIAC CATHETERIZATION—A DIAGNOSTIC AID IN CONGENITAL HEART DISEASE. J. H. LEHMANN, A. D. JOHNSON, W. C. BRIDGES, J. MICHEL, and D. M. GREEN, Northwest Med. **50**:170 (March) 1951.

This is a short article relating the experiences of the authors with cardiac catheterization in the diagnosis of congenital heart disease. Five reasons for undertaking this procedure in selected patients are outlined. The principle of Fick as it is employed in the calculation of cardiac output, pulmonic blood flow, and blood flow in shunts is discussed rather thoroughly. The method of the cardiac catheterization is briefly outlined. The article concludes with roentgenograms, illustrative diagrams, and analyses of the data obtained in seven specific cases wherein cardiac catheterizations were a definite aid in localizing congenital heart defects.

DOCTER, Seattle.

THE RH FACTOR IN OBSTETRICS. MARTIN S. SICHEL, Northwest Med. **50**:181 (March) 1951.

In spite of the title, approximately half of this article relates to treatment of the newborn infant suspected of having erythroblastosis fetalis. The treatment described is that of Diamond as first outlined in 1949, at which time he was advocating exchange transfusion given as soon after delivery as possible if clinical and laboratory signs of erythroblastosis are present at birth, or as soon as symptoms or signs of jaundice or anemia develop.

DOCTER, Seattle.

VARIABLE RESPONSE TO VITAMIN B_{12} OF MEGALOBLASTIC ANEMIA OF INFANCY. CALVIN W. WOODRUFF, HOWARD W. RIPY, J. CYRIL PETERSON and WILLIAM J. DARBY, Pediatrics **4**:723 (Dec.) 1949.

Three patients with megaloblastic anemia of infancy were treated with vitamin B_{12}. The first two patients improved after treatment, and the similar pattern of response in both of them was suggestive of a remission induced by an active hematopoietic agent. This response was in all respects comparable with that obtained with folic acid or liver extracts and was accompanied with a clinical improvement characterized by greatly increased appetite, disappearance of apathetic attitude, increase in activity, and other less tangible reactions. The third patient failed to respond to vitamin B_{12}. This patient had a definite celiac reaction. That this failure was not conditioned by the septicemia which developed is indicated by the fact that the patient later responded to folic acid despite a moderately severe respiratory infection.

These observations imply that the megaloblastic anemia of infancy may not be a single entity, but, rather, a syndrome, some cases of which may respond to one of the newer hemopoietic vitamins, while other cases respond to another. The relationship between these two factors is as yet obscure.

FROM THE AUTHORS' SUMMARY.

DOUBLE AORTIC ARCH: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE. HERBERT E. GRISWOLD JR. and MAURICE D. YOUNG, Pediatrics **4**:751 (Dec.) 1949.

The anatomic nature of a double aortic arch is described. Reference is made to the history of the malformation. The clinical picture and roentgenographic findings described by various authors are discussed. Two cases are reported which demonstrate two types of double aortic arch. In one case, a relatively common type, the patient had a large right arch with a retroesophageal component and a left descending aorta; in the second, a rare type, the patient had a large left arch with a retroesophageal component and a right descending aorta. Further, one patient was an infant who had symptoms of constriction, whereas the other was an adult who had no symptoms referable to the double aortic arch.

Analysis is made of these cases and 47 other cases reported in the literature. This analysis reveals the following:

1. There is a striking correlation between the occurrence of symptoms and the age and duration of life, but there is no correlation between the occurrence of symptoms and the specific anatomy of the arch.

2. A double aortic arch in which both components are patent throughout is likelier to produce symptoms than a double aortic arch in which one component is partially obliterated. The process of obliteration does not appear to give rise to symptoms.

3. There is considerable variation in the relative sizes of the components of a double aortic arch. The right component is usually the larger; part of the left component may be obliterated. To date, no case has been reported of obliteration of part of a persistent right component.

4. A double aortic arch occurs more commonly with a left descending aorta than with a right descending aorta.

5. It is unusual for a double aortic arch to be associated with a malformation of the heart. The association of a double aortic arch with other vascular abnormalities is less rare.

The two principal problems raised by the demonstration of a retroesophageal vessel are discussed. The first concerns the nature of the malformation; the second concerns the advisability of operation in the given patient.

FROM THE AUTHORS' SUMMARY.

OCCURRENCE OF INNOCENT ADVENTITIOUS CARDIAC SOUNDS IN CHILDHOOD. SIDNEY FRIEDMAN, WILLIAM A. KOBIE, and T. N. HARRIS, Pediatrics **4**:782 (Dec.) 1949.

Five hundred children between the ages of 2 and 12 were subjected to a special cardiac examination. Of these, 234 (46.8%) were found to have functional cardiac murmurs and 137 (27.4%) were found to have extracardiac sounds. There was a considerable degree of association between the occurrence of these two types of adventitious sounds. Neither, however, was found to be correlated with the degree of anemia present, the age, color, sex, state of nutrition, or the temperature of the subjects examined.

A strong association was found to exist between the quality of many functional cardiac murmurs and their point of maximal intensity over the precordium, those in the midprecordium being commonly of the vibratory type and those in the pulmonic region of the blowing variety.

The most valuable criteria for the differentiation of functional from organic cardiac murmurs in childhood are the acoustic quality and the point of maximal intensity of the murmur.

FROM THE AUTHORS' SUMMARY

PERNICIOUS ANEMIA IN AN EIGHT YEAR OLD GIRL: ADDITIONAL OBSERVATIONS IN A CASE PREVIOUSLY REPORTED AS "NUTRITIONAL ANEMIA IN AN INFANT RESPONDING TO PURIFIED LIVER EXTRACT." LEONARD ROSENZWEIG and OGDEN C. BRUTON, Pediatrics **6**:269 (Aug.) 1950.

A progress report on an 8-year-old girl for whom the diagnosis of "nutritional anemia" was made when she was 4 months of age is presented. The child exhibited macrocytic anemia, megaloblastic bone marrow, achlorhydria resistant to histamine, and atrophy of the papillae of the tongue. There were no neurologic symptoms or signs. Treatment with folic acid resulted in reticulocytosis with remission of the anemia and conversion of the bone marrow to a normoblastic pattern. Withdrawal of the folic acid therapy resulted in a relapse which was successfully treated with vitamin B_{12}.

It is felt that this case fulfills the necessary criteria for the diagnosis of pernicious anemia, and because of the rare occurrence of the disease in childhood, it is reported as an additional instance.

FROM THE AUTHORS' SUMMARY.

ELECTROENCEPHALOGRAPHIC FINDINGS IN SICKLE CELL ANEMIA. JAMES G. HUGHES, FONTAINE S. HILL, and BILLIE CAMP DAVIS, Pediatrics **6**:277 (Aug.) 1950.

Electroencephalographic findings in 38 cases of sickle cell anemia are presented, of which 35 cases were in children under 14 years of age. The electroencephalograms were considered to be abnormal in 26 patients. Of special interest was the fact that all children under 6 years of age had abnormal electroencephalograms. In the group as a whole, there were nine patients with a past history or the presence of nervous system symptoms who had normal electroencephalograms and three whose tracings were thought to be borderline.

A brief review of the principal pathologic changes in the brain in sickle cell anemia is presented, and a discussion is given of the way in which these changes might influence brain

potentials. Abnormal brain potentials in patients with sickle cell anemia are considered to be due primarily to cerebral anoxia and secondarily to degenerative processes in nerve cells.

Electroencephalography offers a new approach to the determination of the incidence and character of cerebral dysfunction in sickle cell disease. FROM THE AUTHORS' SUMMARY.

ANGIOCARDIOGRAPHY IN CONGENITAL HEART DISEASE OF CYANOTIC TYPE: II. OBSERVATIONS ON TRICUSPID STENOSIS OR ATRESIA WITH HYPOPLASIA OF THE RIGHT VENTRICLE. ROBERT N. COOLEY, ROBERT D. SLOAN, C. ROLLINS HANLON, and HENRY T. BAHNSON, Radiology **54**:848 (June) 1950.

The findings in 21 cases of tricuspid stenosis or atresia were reviewed. The most significant x-ray finding was nonvisualization of the right ventricle. The presence or absence of transposition of the great vessels was satisfactorily ascertained. The presence of an interauricular septal defect was inferred in five illustrated cases and was directly demonstrated in three. Attention is called to the fact that nonvisualization does not always indicate absence of the right ventricle. Roentgenograms made in the lateral projection were the most dependable in showing this defect.

ANSPACH, Chicago.

A CASE OF FAT EMBOLISM IN EARLY CHILDHOOD. H. G. HOWELL RICHARDS, Edinburgh M. J. **52**:252 (June) 1950.

A 2½-year-old girl had congenital dislocation of the hips. She was given nitrous oxide and ether, and manipulation was attempted, but during this procedure she sustained a fracture of the right femur. Within a few hours her pulse rate began to rise, and she became cyanotic. Respiratory distress developed, and the child died 16 hours after the accident. At autopsy fat globules were found in the pulmonary vessels, the kidney, and the heart. In the heart fat emboli were found in the interstitial capillaries, and tiny fat globules were found in the muscle fibers. Richards suggests that the fat in the fibers was due to phanerosis as a result of impaired blood supply. The pathogenesis of fat emboli is discussed.

MACDONALD, Pittsburgh.

COARCTATION OF THE AORTA ASSOCIATED WITH PERSISTENT DUCTUS ARTERIOSUS. P. SOULIE, M. SERVELLE, J. HOREAU, and J. NOUAILLE, Presse méd. **58**:137 (Feb. 11) 1950.

A routine examination of a 14-year-old girl revealed congenital heart disease. Although she had no complaints, she admitted to some dyspnea at play and, during the past six months, occasional palpitations. A continuous thrill was present over the third left interspace; a continuous murmur was heard at the second and third left interspaces, and a loud systolic murmur was present at the apex. No pulsation could be obtained over the femoral arteries, while evidence of vascular dilatation of the vessels of the thorax was visible. There was no cyanosis ot the lower extremities. Costal erosion appeared on the roentgenograms, together with the cardiac formation seen with patent ductus arteriosus. Cardiac angiography confirmed the clinical impression of coarctation of the aorta, with a patent ductus arteriosus proximal to the site of constriction. This location is unusual. Operation was performed successfully.

DAFFINEE, Melrose, Mass.

SPLENOMEGALY IN PERNICIOSIFORM ANEMIA IN INFANTS. A. FERLAZZO, Lattante **21**:553 (Sept.) 1950.

Two infants, both 13 months of age, had very large spleens and blood pictures suggestive of pernicious anemia. The anemia responded to a good diet and liver preparations. The author believes that this pattern makes a new category of perniciosiform anemia.

HIGGINS, Boston.

PATHOGENESIS OF THE HEMORRHAGIC SYNDROMES. E. COMOLLI, Minerva pediat. **2**:312 (July) 1950.

The various hemorrhagic diseases seen in children are discussed; case reports are presented illustrating the various types of purpura, especially those associated with infections and toxemia and those associated with functional vascular dyscrasias.

HIGGINS, Boston.

SEROLOGICAL STUDIES ON ANTIGENIC POTENCY OF HEMOGLOBINS OF COOLEY'S ANEMIA AND OF SICKLE-CELL ANEMIA. F. VECCHIO and E. BARBAGALLO, Pediatria **58**:481 (July) 1950.

Observations with rabbits indicate that the hemoglobin of the blood of patients with familial erythroblastic (Cooley's) anemia contains two antigens, one being that found in the hemoglobin of normal blood and the other that found in the hemoglobin of blood obtained from the umbilical cord of the newborn (probably fetal hemoglobin). Only one antigen was found in the hemoglobin of the blood of patients with sickle-cell anemia: that found in the hemoglobin of normal blood.

HIGGINS, Boston.

CASE OF NONSPECIFIC PERICARDITIS. PEDRO DANIEL MARTINEZ and CARLOS SARINANA, Bol. méd. Hosp. inf., México **7**:717 (Oct.) 1950.

The authors present a case of nonspecific acute pericarditis with effusion in a 3-month-old boy in whom all other causes of pericarditis were eliminated. The patient recovered spontaneously after three months. No results were obtained with the therapeutics instituted when sulfadiazine, penicillin, streptomycin, and aureomycin were used. FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat, and Ear

ELECTROENCEPHALOGRAPHY IN THE DIAGNOSIS OF HEARING LOSS IN THE VERY YOUNG CHILD. R. E. MARCUS, E. L. GIBBS, and F. A. GIBBS, Dis. Nerv. System **10**:170 (June) 1949.

Education of the hearing-handicapped child, to be effective, must be instituted early, but the diagnosis of profound deafness in the very young is clinically difficult. The authors report an approach utilizing the "arousal response" (waking activity interrupting cortical sleep patterns) in the electroencephalogram of the sleeping child. Various loud, frightening noises were produced, and it was observed that the "arousal response" was obtained when the sound was perceived and was the same as that caused by other types of sensory stimulation. Nineteen patients, from 17 months to 9 years of age, were studied; in 13 no audition could be demonstrated by routine otological testing. Four of the latter group showed some "arousal response." It is concluded that electroencephalography provides a technic for the diagnosis of deafness in the infant and child and that the "arousal response" to appropriate stimuli is an adequate index of hearing. As an additional observation, it was found that of the 13 children with recognized deafness, seven had electroencephalographic abnormality. The remaining six patients, in whom the primary disorder was retarded speech and an associated incomplete reduction in auditory function, all displayed electroencephalographic irregularities. The relation of hearing loss to disorders of the central nervous system should receive further investigation.

BEATON, Tucson, Ariz. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

AN ANALYSIS OF HEARING LOSS PATTERNS IN A RURAL ILLINOIS SCHOOL SYSTEM. E. THAYER CURRY, Eye, Ear, Nose & Throat Month. **29**:357 (July) 1950.

A report is given of a statistical analysis of hearing loss patterns made during the spring of 1949 in a school system in central Illinois. Tests were performed with pure-tone audiometry. For the screening technique a pure-frequency sweep test was utilized at 15 db. intensity at the seven frequencies 256, 512, 1024, 4096, 8192, and 11584. All persons who failed to pass this sweep test were given an individual audiometric test. Hearing loss was defined as a failure to respond to a tone as loud as 30 db. in either ear in any of the seven test frequencies.

Curry draws the following conclusions relative to the hearing characteristics of this group of 1,217 students in grades 5, 7, and 9: There is a statistical difference between incidence of hearing loss in boys and girls, as the occurrence in boys was 15.29% and in girls 10.10%. There was no statistical difference in the percentage of occurrence of hearing loss in the three grades tested. The tendency for loss of hearing to occur oftener in the right ear than in the left, noted consistently in the data, is not statistically significant. It is noted that a tendency exists for monaural hearing loss to occur oftener than binaural hearing loss and that this tendency is greater among boys than among girls.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

NEOMYCIN IN THE TREATMENT OF OTITIS MEDIA IN INFANTS. A. M. LAZAR and J. FISHMAN, Eye, Ear, Nose & Throat Month. **29**::484 (Sept.) 1950.

Lazar and Fishman describe a syndrome encountered in infants under 3 months of age. The children are poor feeders, restless, poor sleepers, cry a great deal, and do not gain any weight. There is a low-grade temperature elevation with an associated diarrhea. A thorough examination reveals aural signs of an otitis media; often there is a red bulging eardrum membrane. Paracentesis provides immediate relief. The culture frequently reveals Pseudomonas aeruginosa. Often the nose and nasopharynx appear normal but on culture reveal the same organisms as the ear. The usual otitis of infants can be treated very easily by the antibiotics now in use, but the middle ear infection caused by Ps. aeruginosa presents a problem. The authors have experienced gratifying results with the use of a new antibiotic, neomycin, a preliminary report of which they present in this article.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

ROLE OF THE VESTIBULAR APPARATUS IN THE PRODUCTION OF NAUSEA AND VOMITING FOLLOWING THE ADMINISTRATION OF MORPHINE TO MAN. A. RUBIN and J. WINSTON, J. Clin Invest. **29**:1261 (Oct.) 1950.

Morphine has among its disturbing side-effects the production of nausea and emesis. Studies have suggested that morphine may disturb vestibular function and that the vestibular activity incident to ambulation may then result in an increase in nausea and emesis. To investigate this possibility, the authors examined the responses to vestibular stimulation in 20 healthy adults before and after the administration of morphine.

It was found that morphine sulfate produced a significant decrease in vestibular response. Vestibular stimulation following the administration of morphine sulfate resulted in a notable increase in nausea and emesis. Amphetamine sulfate was of no apparent benefit in relieving this emesis. Dimenhydrinate, given either orally or rectally, appeared to prevent and relieve nausea, vomiting, and vertigo following morphine, dihydromorphinone (dilaudid®), and meperidine, and its use therapeutically and prophylactically with these drugs is suggested.

Neither dimenhydrinate nor amphetamine altered the vestibular changes produced by morphine. Vestibular changes following morphine resulted in no significant changes in blood pressure or pulse rate.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE INCIDENCE OF CONGENITAL IMPATENCY OF THE NASOLACRIMAL DUCT. EDWIN L. KENDIG JR. and DUPONT GUERRY III, J. Pediat. **36**:212 (Feb.) 1950.

Congenital impatency of the nasolacrimal duct was found in 5.7% of 1,000 newborn infants. In most of these patients the condition cleared with local application of penicillin ophthalmic ointment and massage of the lacrimal sac. If patency has not been established by the age of 6 months, the duct should be probed.

MACDONALD, Pittsburgh [A. M. A. ARCH. OTOLARYNG.].

SOME BASIC CONSIDERATIONS IN TEACHING LANGUAGE TO THE DEAF. LOUIS M. DICARLO, J. Speech & Hearing Disorders **14**:247, 1949.

Deaf children show deficiencies in all types of linguistic performances. Skill for adequate language adjustment begins shortly after birth. When deafness compels a child to develop meanings through other sensory and motor avenues, his language responses take on a fragmentary character which fails to satisfy his motives. Language instruction of deaf children must integrate all aspects of the communication arts. Vocabulary teaching to deaf children should follow the normal vocabulary development of normal children, since much high-level language is presented too early, and the consequential mechanical reply lacks meaning. Reading and writing similarly should be developed through context and meaning, with avoidance of single-word stimuli and other hampering procedures. If language material is presented properly, pupil interest, purpose, and motivation will merge.

PALMER, Wichita, Kan.

WORKING WITH PARENTS OF STUTTERING CHILDREN. HILDRED SCHUELL, J. Speech & Hearing Disorders **14**:251, 1949.

Parents of stuttering children are not a homogeneous group. A series of interviews with parents of stuttering children should be planned by the speech correctionist. The first interview by appointment should gain as much information as possible about the parent and is more effective with only one parent present. The Vineland Social Maturity Scale is often helpful, and plans at the first interview should be made for a follow-up. The second interview elicits the ideas which parents have about stuttering, and assignments are made for them to do something constructive concerning the situation. For example, parents should give the child opportunities to talk to them every day and instruct other members of the family not to make comments about the child's speech. Parents may report on given forms the amount of stuttering which occurs in certain situations. In the third interview, the speech correctionist is able to go over with the parents the data gathered by these assignments and from these and from the parents' comments develop further planning. Parental insight often develops slowly. Parents need to plan a definite period during the day when a child can have time with one or both parents, and the child must have a program from which will develop confidence in some particular activity. Situations must be planned which will help the child develop confidence in his ability to talk. Subsequent interviews should be made as the necessity arises. Parental interviews are an important, but partial, clinical issue.

PALMER, Wichita, Kan.

REHABILITATION: THE OTOLARYNGOLOGIST AND AUDIOLOGY. FRANCIS L. LEDERER and RICHARD E. MARCUS, New York J. Med. **50**:2407 (Oct. 15) 1950.

Lederer and Marcus quote Canfield's definition of audiology, which says that audiology is concerned with the propagation of sound, its conduction to the ear, its "fate" thereafter, and the psychological processes which interpret it in the brain. The inference is that many otologists are not well grounded in audiology in the broad sense and in its modern relation to allied sciences, particularly to speech as concerned with rehabilitation. Audiology is now a "basic science" and includes speech audiometry for interpretation of reception and discrimination levels, auditory reeducation, speech-reading ability, visual competence, group tests for screening of speech defects in schools, evaluation of hearing aids for the very young and very old, integration with acoustics, electronics, physiology, and instruction of parents, nurses, and others who live close to the child in his daily life. Since this is a very wide subject, the matter is being taken over by lay or nonmedical persons, who find in it a means of livelihood.

In the discussion, Dr. G. M. Trainor of Rochester, N. Y., recommended that otologists visit Veterans Administration centers to observe what is being done with this rehabilitation problem. He also stressed a better understanding of "fitting aids" to the deaf person so that the otologist can consult with and advise the patient of his needs. Dr. Alfred Doust of Syracuse, N. Y., said that since 1946 Syracuse has had a conservation of hearing center under the leadership of Dr. Gordon Hoople.

VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

UNILATERAL DEAFNESS AND PROGRESSIVE FACIAL PALSY DUE TO INTRAPETROUS NEUROFIBROMA. J. GRAFTON LOVE, Proc. Staff Meet., Mayo Clin. **25**:228 (April 26) 1950.

Love reports the case of a girl aged 16 with deafness in the right ear of eight years' duration and progressive paralysis of the right side of the face for two and one-half years. The roentgenologic picture was that of an intrapetrous epidermoid. At operation the tumor was found entirely within the petrous bone. It proved to be a neurofibroma, very fibrous in type. Presumably, the tumor had taken its origin from the eighth cranial nerve within the petrous bone, and it never at any time presented in the cerebellopontile angle, as tumors of the eighth nerve usually do.

The facial paralysis and loss of hearing were unaltered by operation. One month after the first operation a spinofacial anastomosis on the right side was carried out. Three months later there was no definite clinical evidence of reinnervation except for possible slight movement about the right corner of the mouth and below the nose. Fourteen months later there was pronounced improvement, with movement of all facial muscles, including the forehead.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CHRONIC MAXILLARY SINUSITIS IN THE INFANT. MASPÉTIOL, CHAUVET, and CARRÉ, Ann. oto.-laryng. **67**:758 (Nov.-Dec.) 1950.

Contrary to the common impression and general belief, isolated chronic sinusitis without ethmoidal involvements is relatively frequent in the infant. In fact, it is more frequent in the infant than ethmoiditis.

A study of 202 roentgenograms demonstrated the following findings: (1) roentgenologic evidence of involvements of the maxillary sinus in 114 patients without evident ethmoidal infection, (2) ethmomaxillary involvement in 12, and (3) ethmoidal opacity alone in 6. Diagnostic punctures in 41 patients revealed positive findings in 28.

Chronic maxillary sinusitis is often overlooked owing to the fact that the functional rhinopharyngeal signs are not striking. The usual rhinoscopic signs of sinusitis are generally absent. A definite diagnosis can be obtained only by routine and systematic roentgenograms and antral punctures when indicated.

VIOLE, Los Angeles [A. M. A. ARCH. OTOLARYNG.].

BROMIDE-IODIDE THERAPY IN DISEASES OF THE TONSILS OF CHILDREN. L. LANDUCCI, Clin. Pediat. **33**:117 (March) 1951.

Children with diseased tonsils have been treated by hydrotherapy at a bath house with mineral water containing bromides and iodides. Most of the 600 thus treated showed improvement after a period of 15 days. A tonsillar test is described: the white blood cell count is made before and 60 minutes after each tonsil has received a three-minute digital massage. The reaction is regarded as positive, and indicative of infection, if the white cell count has shown an increase or decrease of more than 1,000. Of 30 children tested, all gave a positive reaction before the hydrotherapy was begun. Only eight of them gave a positive reaction at the end of the course of hydrotherapy. The author ascribes the benefit of the treatments to a general constitutional reaction rather than to local effect on the tonsils.

HIGGINS, Boston.

HISTOPATHOLOGICAL STUDY OF TONSILS IN CHILDREN. T. PORCELLI, Minerva pediat. **2**:593 (Dec.) 1950.

From a careful study of the tonsils of 42 children the author has concluded that it is impossible anatomically to distinguish between simple hyperplasia and hyperplasia due to previous inflammation. He found no histological picture characteristic of any specific disease.

HIGGINS, Boston.

THE AGE FACTOR IN TONSILLECTOMY. PEDRO FALCAO, Rev. Brasil, oto-rino-laring. **18**:1, 1950.

Falcao considers age as of secondary importance in tonsillectomy. Clinical indications should be the index for the decision for surgical intervention. He has performed tonsillectomies on patients ranging from the age of 12 months to 75 years. While he believes that the ideal age is between 3 and 5 years, factors which would interfere with the normal development of the child or factors which might lead to serious systemic conditions, such as acute rheumatic fever and other complications, influence his decision as to earlier surgical intervention. With careful technique and particularly intracapsular dissection, Falcao believes that very little trauma occurs and that tonsillectomy can be performed at any time and at any age. In the younger children he frequently uses antibiotics in the acute stages of tonsillitis until the child is 3 to 5 years of age. For those with chronic tonsillitis he uses a mixture of protein, bismuth, and calcium.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura, and Mediastinum

A SIMPLE, SAFE BRONCHOGRAPHIC TECHNIQUE FOR CHILDREN. JOSEPH B. MILLER and WILLIAM H. CONYERS JR., J. Pediat. **36**:721 (June) 1950.

Miller and his colleagues have simplified bronchography by using an aerosol anesthetic containing 0.5% tetracaine (pontocaine®) hydrochloride with epinephrine and a detergent (triton® A-20) for its spreading and penetrating qualities. To this they have added a droplet stabilizer,

glycerin. With this anesthetic, iodized oil (lipiodol®) can be dropped into the trachea without catheterization. No fluoroscope and no endoscopic instruments are required. The anesthesia and the entire procedure, as described in detail by the authors, are safe, simple, and easy.

MACDONALD, Pittsburgh.

LOBAR AGENESIS OF THE LUNG. DOUGLAS R. MORTON, KARL P. KLASSEN, and EARL BAXTER. J. Thoracic Surg. **20**:665 (Oct.) 1950.

Agenesis of the lung is an uncommon developmental anomaly. However, since 1937, about 75 cases have been reported in the literature. Lobar agenesis with associated abnormality of the bronchotracheal tree is so extremely rare that it appears to have escaped specific mention. The authors subscribe to the classification of pulmonary agenesis proposed by Schneider in 1912: (1) agenesis of lung, in which there is complete absence of the lung and bronchi; (2) aplasia of lung, in which there is a rudimentary bronchus but no pulmonary alveolar tissue; (3) hypoplasia of lung, in which pulmonary tissue is underdeveloped in the whole lung or in part of a lung.

Two cases, one proved by exploratory thoracotomy and the other by autopsy, of lobar agenesis are reported, with agenesis of the upper and middle lobes of the right lung. The first patient, 11 years of age, had frequent colds and a persistent cough for several years and had recently been experiencing increasing dyspnea. The second patient, 2 months old, seen at the hospital because of persistent vomiting since birth, died soon after admission.

It is believed that the abnormality in bronchial development must occur between the 5-mm. and 7-mm. stages of the human embryo. Congenital pulmonary malformations are frequently associated with other congenital anomalies, including esophageal atresia and tracheoesophageal fistula.

MEYER, Chicago.

TREATMENT OF PNEUMONIAS IN CHILDREN WITH A SINGLE MASSIVE DOSE OF SULFATHIAZOLE. C. FRIDERICHSEN and T. WALTHER, Ann. pædiat. **175**:285 (Oct.) 1950.

A single massive dose of sulfathiazole was used in the treatment of 1,500 children; 875 had pneumonia and were under 11 years of age. No harmful effect of the treatment on either blood or kidneys was observed. One dose of 0.30 gm. of sulfathiazole per kilogram of body weight was given; for over 13 kilogram of body weight 4 gm. was the maximum dose. In the cases of severe pneumonia the dose must sometimes be repeated after 24 to 48 hours. The total mortality was 4.9%; the reduced mortality was found to be 0.5%. A single massive dose gives better results than continuous treatment with the drug.

FROM THE AUTHORS' SUMMARY.

THE ROLE OF OVERVENTILATION IN DISEASES OF INFANCY. S. RAPOPORT, Ann. pædiat. **176**:137 (March) 1951.

The frequent occurrence and clinical importance of hyperventilation in diseases of infants is illustrated with data from 47 patients. Hyperventilation, occasionally difficult to assess clinically, is indicated by low values of carbon dioxide tension. Its pathologic effects arise partly from loss of carbon dioxide, but in a larger measure from the loss of water unaccompanied with solutes. The effects include oliguria, hyperosmolarity and hyperelectrolytemia, pyrexia, vascular collapse, and frequently convulsions and hypocalcemia. Among the clinical conditions cited in which hyperventilation has a dominant role are (1) the "infantile hyperventilation syndrome," of as yet unknown etiology, (2) certain cases of pneumonic infection, and (3) salicylism in infants. In several other pathologic states hyperventilation is a subsidiary factor. Examples cited include diarrhea, septicemia, congenital heart disease, and extensive burns. The therapeutic implications of a state of hyperventilation are discussed.

FROM THE AUTHOR'S SUMMARY.

ACUTE BULLOUS EMPHYSEMA (PSEUDOCAVITIES) IN THE COURSE OF BRONCHOPNEUMONIA IN CHILDREN. C. STICCA, Minerva pediat. **2**:576 (Dec.) 1950.

A child with bronchopneumonia showed large emphysematous blebs on roentgenography. These blebs gradually disappeared as the patient convalesced.

HIGGINS, Boston.

CLINICAL STATISTICS REGARDING ACUTE RESPIRATORY INFECTIONS SEEN IN THE PEDIATRIC CLINIC OF NAPLES IN THE 20-YEAR PERIOD 1930-1949. P. DE CAPRIO, Pediatria **59**:5 (Jan.) 1951.

This 63-page article gives statistics as to 841 cases of pneumonia in infants and children and compares the cases of the first decade, 1930-1939, with those of the second, 1940-1949. Malnutrition seemed to play a considerable role for many of the children being susceptible to the disease; 10% of the pneumonia patients were syphilitic. The highest incidence of pneumonia was in the month of June, and the next highest was in November. The number of cases had dropped from 572 in the first decade to 269 in the second. In the second decade the relative incidence of pneumonia was much higher among children under 2 years of age; but the number of complications in this decade were fewer, except for meningitis, and the mortality was markedly lower.

HIGGINS, Boston.

SYNDROME OF MARKED MEDIASTINAL COMPRESSION IN A CASE OF DIFFUSE ANGIOMATOSIS. G. ACETO, Pediatria **59**:236 (March) 1951.

In a 26-month-old child with several subcutaneous angiomas the more noticeable being on the cheek and back, a marked suprasternal swelling and considerable difficulty in breathing developed. The probable diagnosis was a mediastinal angioma, possibly cavernous. The various possibilities in the differential diagnosis are considered. Radium or x-ray therapy was advised, but family objections prevented further follow-up of the case.

HIGGINS, Boston.

USE OF ANTIBIOTIC SPRAYS OR INHALATIONS IN PEDIATRICS. JOSE SELFA, Acta pediat. espan. **86**:143 (Feb.) 1950.

After reviewing the findings of Segal, Bryson, Kruege, and Barach on the use of penicillin by inhalation, the author reports additional excellent results in children suffering from bronchiectasis, chronic bronchitis, tracheitis, and asthmatic bronchitis who have been resistant to the usual antiallergic treatments. He found the blood levels as satisfactory as those obtained with other methods of penicillin administration. None of the children showed toxic reactions or intolerance to the drug.

For children who could cooperate he used the apparatus made in America which is called the premonebulizer; for small babies a special apparatus which, from the picture accompanying the article, resembles an oxygen tent and respirator was used. For children with asthma of an allergic nature he followed the treatment with the Vaponefrin nebulizer, using a solution of 2.25% hydrochloride of epinephrine in purified racemic form. This was further diluted 1:100 and given by means of a spray or nebulizer. The children with bronchospasm had this added, and there were only three of the 76 who needed it.

ALLEN, Santa Fe, N. M.

NEUROPSYCHICAL DISORDERS IN CONSEQUENCE OF PNEUMONIA IN CHILDREN. M. SCHACHTER, Paediat. danub. **6**:193 (Oct.-Dec.) 1949.

Different disturbances of the nervous system and the brain that may occur as sequelae of pulmonary infections and bronchopneumonia are discussed, and seven cases are reported. Encephalitic symptoms appearing during pulmonary disease are especially indicative of probable appearance of late lesions of the central nervous system and of disturbances of mental development. The early recognition of such cases is of great importance for suitable medical and pedagogic measures to be applied in time.

FROM THE AUTHOR'S SUMMARY.

MALIGNANT TERATOMA OF ANTERIOR MEDIASTINUM IN A TWO-YEAR-OLD CHILD. J. SVEJDA and Z. BRUNECKY, pediat. listy **5**:218 (No. 4) 1950.

Malignant teratoma of the anterior mediastinum in a 2-year-old girl is described. A great part of the tumor was necrotic, and there were metastases in the upper and lower lobe of the right lung and the lower lobe of the left lung. Histologically the tumor consisted of lung, cerebral, fibrous, arteriovenous, and cartilaginous tissue. In the malignant parts anaplastic carcinomatous tissue with a partly adenomatous arrangement of the cells was found.

FROM THE AUTHORS' SUMMARY.

REPORT OF 20 CASES OF PRIMARY ATYPICAL PNEUMONIA IN INFANTS TREATED WITH AUREOMYCIN. J. SIRCHICH and M. RAKOVSKA, pediat. listy **5**:219 (No. 4) 1950.

Twenty cases of primary atypical pneumonia in infants are described. The course of the disease was relatively benign, when the age of the children is considered. Aureomycin was used with excellent results.

FROM THE AUTHORS' SUMMARY.

INTERSTITIAL PLASMA CELL PNEUMONIA. THEODOR WALTHER, Acta pædiat. **39**:545 (No. 6) 1950.

Walther gives a report of two cases of interstitial plasma cell pneumonia.

FROM THE AUTHOR'S SUMMARY.

ON CONGENITAL PNEUMONIA. E. K. AHVENAINEN, Acta pædiat. **40**:1 (Jan.) 1951.

Pneumonia was found microscopically in 14 of 45 cases of stillbirth. There was no difference between full-term infants and premature infants.

Prolonged delivery, infections of the mother, and early ruptures of membranes are often seen in pneumonia cases, but pneumonia can develop even in cases without any complications during labor.

As a cause of fetal death pneumonia is rare. According to this material, in the etiology of pneumonia of the newborn congenital pneumonia is an important factor to be taken into account. This knowledge is also of importance to the clinician.

FROM THE AUTHOR'S SUMMARY.

ACUTE INFECTIOUS ATELECTASIS SIMULATING BRONCHOPNEUMONIA IN INFANTS. T. JERSILD and N. RISKAER, Acta pædiat. **40**:24 (Jan.) 1951.

The development of acute infectious atelectasis is pointed out as a contributory cause of the strikingly high death rate from pneumonia in infancy. The records of two characteristic cases are reported. A brief review is given of the autopsy records for 178 children who died with the diagnoses of pneumonia, bronchitis, or laryngotracheobronchitis; the presence of atelectasis was shown in 43%. The diagnosis and treatment are discussed. It is emphasized that administration of sulfonamides or antibiotics is not sufficient and that repeated bronchoscopy with aspiration is required in order to avoid suffocation in the most critical phase.

FROM THE AUTHORS' SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

OBSERVATIONS ON A SMALL OUTBREAK OF INFANTILE DIARRHEA ASSOCIATED WITH PSEUDOMONAS AERUGINOSA. ALFRED L. FLORMAN and NATHAN SCHIFRIN, J. Pediatrics **36**:758 (June) 1950.

Florman and Schifrin report a small outbreak of diarrhea in a nursery. Pseudomonas aeruginosa was recovered from the stools of five patients. The authors were unable to differentiate clearly the strains of these organisms from Ps. aeruginosa obtained from other sources. However, strains obtained from four of the five patients with diarrhea were serologically homologous and identical with the strain recovered from the hands of a nurse attendant. The organism obtained from one patient with diarrhea was in a serologic group of its own. The serums of convalescing infants contained no agglutinins for their homologous organism.

Soaking the contaminated objects in the nursery in 70% ethyl alcohol for two minutes effectively removed Ps. aeruginosa. Oral polymyxin B seemed to be more effective than other antibiotics in treatment.

MACDONALD, Pittsburgh.

DEHYDRATED BANANA IN THE DIETETIC MANAGEMENT OF DIARRHEAS OF INFANCY. JOSEPH H. FRIES, and NICHOLAS J. CHIARA, J. Pediat. **37**:367 (Sept.) 1950.

Forty infants with nonspecific diarrhea were studied. Stool cultures, agglutination tests, and blood cultures failed to indicate any specific etiologic agent. These infants were divided into two groups. The control group of 20 infants were not fed for 24 to 48 hours and sustained

during this time by clysis. After this, the feedings of these infants were gradually resumed, with a variety of protein and acidified milks being given. The 20 infants in the other group were started on banana powders in water immediately; there was no starvation period for these. After 48 to 72 hours they were given banana powder in skim milk. They received clysis when necessary. The banana-powder mixture was well tolerated, and the infants thus treated gained weight more frequently and recovered more rapidly than the infants in the control group.

MACDONALD, Pittsburgh.

CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEOESOPHAGEAL FISTULA. WILLIS J. POTTS, J. Thoracic Surg. **20**:671 (Nov.) 1950.

A diagnosis of tracheoesophageal fistula should be considered for all newborn children who breathe poorly immediately after birth, have excessive mucus of the mouth and throat, and have cyanotic spells during the early hours after delivery. Confirmation of the deformity may be made by introduction of 2 or 3 cc. of iodized oil (lipiodol®) through a catheter into the upper end of the esophagus and by taking a roentgenogram.

This article reviews 35 cases of atresia of the esophagus with and without tracheoesophageal fistula. Prematurity and multiple congenital deformities increase the hazard of operation. The majority of infants had pneumonia and/or atelectasis at the time of operation. Three of the 35 infants had atresia of the esophagus without tracheoesophageal fistula. The remaining 32 infants had atresia of the upper end of the esophagus with fistulous communication of the lower end of the esophagus at or near the carina (Type 3). Twenty-five patients in this group were treated by primary end-to-end anastomosis of the esophagus; 11 survived the operative procedure.

Preoperative feeding and hydration of these patients is a difficult problem. Blood transfusion, antibiotic therapy, and repeated pharyngeal aspiration are of great importance. The operative procedure is described. In the presence of marked leakage through the posterior wound postoperatively, gastrostomy must be done. Postoperative esophageal stricture is a frequent complication in this group, and often it requires dilatation either by antegrade or retrograde methods.

MEYER, Chicago.

CONGENITAL ATRESIA OF THE ESOPHAGUS: ANTETHORACIC PLACEMENT OF THE STOMACH FOLLOWED BY INTRATHORACIC TRANSPLANTATION. WILLIS J. POTTS, J. Thoracic Surg. **20**:681 (Nov.) 1950.

In cases of congenital atresia of the esophagus without tracheoesophageal fistula it is often impossible to bring the short distal segment up to the proximal segment. The author reports a case in which approximation was not possible. Two days later gastrostomy was performed. Because transplantation of the stomach into the chest was contemplated, esophagostomy was delayed. One month later the upper end of the esophagus was exteriorized above the left clavicle. Nine months later, antethoracic subcutaneous transplantation of the stomach was carried out and esophagogastrostomy performed. The subcutaneous stomach functioned well but was large and unsightly. At the age of 22 months the infant was readmitted to the hospital, and the stomach was placed within the left pleural cavity. Although this case terminated successfully, antethoracic placement of the stomach is not advised. Every attempt to approximate proximal and distal esophageal segments should be made before alternative procedures are contemplated.

MEYER, Chicago.

SUPPURATION OF THE SALIVARY GLANDS IN THE NEWBORN. I. NEWTON KUGELMASS, New York J. Med. **51**:613 (March 1) 1951.

Kugelmass states that infection of the salivary glands in newborn infants is not so rare as it is thought to be and cites five references in the literature to prove it. In all five cases reported by him the weight of the infant at birth was from 3 lb. (1,360 gm.) plus to 5 lb. (2,270 gm.) plus. In each instance the physique was frail, and the patient was "overrun with the Staphylococcus aureus in the nasopharynx." Infection was, in each instance, traceable to the mother in whom there was folliculitis or furunculosis, acne, or some other communicable disease due to the Staphylococcus family. It is interesting to note that sulfathiazole failed to prevent suppuration. Penicillin controlled the infection, but the best results were obtained with a combination of

penicillin and chloramphenicol (chloromycetin®). The observations extended over a six-year period. The blood showed a leucocyte count of up to 40,000 per cubic millimeter. The neutrophile count was high—up to 80%. Toward the end of the first week there was unexplained fever, followed by swelling of the parotid or submaxillary glands on one or both sides of the neck. Incision was not required in every case, especially if the antibiotics used were immediately active. Meticulous general care, such as in feeding, was carried out, with excellent results.

VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

CONGENITAL ATRESIA OF OESOPHAGUS. R. H. R. BELSEY and C. P. DONNISON, Brit. M. J. **2**:324 (Aug. 5) 1950.

In 1947 Franklin, in *Lancet*, mentioned that congenital atresia of the esophagus occurred in 1 in 2,500 births. Belsey and Donnison, however, report that in their experience the incidence is much greater than that, being about 1 in 800 deliveries. They state that a number of cases are not diagnosed and that deaths which are due to this condition are attributed to other causes; it is their belief that this condition is even commoner than the above-mentioned figure.

The diagnosis is easy to make if the condition is suspected, and an early sign is the infant's bringing up large amounts of frothy mucus. It is pointed out that it is important that these children should not be fed by mouth until this condition has been excluded. The diagnosis is easily made by the passage of a rubber catheter into the stomach and can be confirmed by roentgenologic studies with a contrast medium.

These authors report 10 patients who were treated by operation; five patients survived. The transpleural approach was used in all five of the successfully treated patients. It is also stated by the authors that feeding by mouth can be resumed 24 hours after operation or earlier and that a gastrostomy appears to be unnecessary in the uncomplicated cases.

BIRDSONG, Charlottesville, Va. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

OESPHAGEAL HIATUS HERNIA. A. V. NEALE, Proc. Roy. Soc. Med. **42**:912 (Nov.) 1949.

A case of esophageal hiatus hernia was reported in a girl aged 7 days. The report is accompanied with roentgenograms showing the large dilation at the lower end of the esophagus after a barium meal and swallow had been given.

WILLIAMSON, New Orleans.

COMPARATIVE STUDY OF SULFONAMIDES IN THE TREATMENT OF INFANTILE DYSPEPSIA. A. K. ABDEL KALEK, A. H. GHOLMY, and M. HANNA, J. Roy. Egyptian M. A. **33**:481 (No. 5) 1950.

Three hundred ninety-five patients with infantile enteritis were treated with varying sulfonamides, including sulfaguanidine, succinylsulfathiazole (sulfasuxidine®), phthalylsulfathiazole (sulfathalidine®), and formaldehyde-sulfathiazole. Results were generally better with the last-mentioned compound.

MCGUIGAN, Evanston, Ill.

SOME CLINICAL OBSERVATIONS ON OTOGENIC DIGESTIVE TROUBLES. P. ROHMER, E. SCHNEEGANS, and C. WILD, Ann. pædiat. **175**:308 (Oct.) 1950.

Based on a few typical examples, this article suggests the relation between otitis and mastoiditis on the one hand and acute gastrointestinal disturbances on the other. The clinical picture is discussed, and conclusions are drawn with regard to treatment.

The authors excluded cases with acute toxicosis because in these other therapeutic measures had to be taken, thus increasing the difficulties in judging the results. But even with them the authors believe that some patients can be saved by timely antrotomy.

FROM THE AUTHORS' SUMMARY.

THRUSH INVOLVING MOUTH, PHARYNX, AND BRONCHI. IDA FRIED, Lattante **21**:531 (Aug.) 1950.

A 4-month-old baby had had pneumonia at the age of 2 months; residual bronchitis persisted, for which penicillin had been frequently administered; occasional attacks of diarrhea had occurred. Thrush developed in the mouth and rapidly extended to the pharynx, the larynx, and the bronchi.

The infant had periods of marked dyspnea and cyanosis. Treatments consisting in administration of aerosols of streptomycin, penicillin, or potassium iodide and penicillin lozenges were ineffective. Local applications of undecylenic acid also appeared ineffective; finally, swabbing of the mouth with boric acid was tried. After 13 days normal breathing was restored, the thrush disappeared, and recovery became complete. Whether any therapeutic procedures, aside from good nursing, were responsible for the relief of the condition is doubtful.

HIGGINS, Boston.

FREQUENCY OF CYSTIC FIBROSIS OF THE PANCREAS. M. BERNARDI and P. MENGHI, Minerva pediat. **2**:572 (Dec.) 1950.

Not one of 45 infants in Milan under one year of age with chronic or recurrent bronchitis had steatorrhea or showed failure of the blood amino acid content to rise after protein feeding. Thus, a diagnosis of cystic fibrosis of the pancreas could be made in none of these children. It is the opinion of the authors that cystic fibrosis of the pancreas is much rarer in Italy than in some other countries.

HIGGINS, Boston.

CONGENITAL MALFORMATIONS OF THE BILE DUCTS AND HEPATIC CIRRHOSIS. U. VIGNOLO-LUTATI, Minerva pediat. **2**:580 (Dec.) 1950.

Two babies, seemingly normal at birth, shortly afterwards became jaundiced, passed acholic stools, and vomited frequently; an enlarged liver developed in both, and both died at the age of about 4 months. Laparotomy in one case revealed that adhesions had prevented the excretion of bile from the liver, while autopsy in the other revealed atresia of the extrahepatic bile ducts and the gall bladder and no ampulla of Vater outlet into the duodenum.

HIGGINS, Boston.

ORAL TREATMENT OF GASTROENTERITIS WITH SULFONAMIDES AND ANTIBIOTICS. G. COLOMBO, Minerva pediat. **3**:159 (March) 1951.

At a Foundling Hospital in Turin, during the years 1945-1950, antibiotics or sulfonamides were used for treating 117 infants, most of them under 6 months of age, with gastroenteritis. Of the 43 given sulfonamide drugs of various types or mixtures, 38 died; of the 55 given penicillin, 20 died; of the 15 given streptomycin, 7 died, and of the 4 given chloramphenicol (chloromycetin®), none died.

The number of patients treated with chloramphenicol were too few to permit any conclusions, but the use of that drug is encouraging. It is recommended that when penicillin is given, it be given orally, mixed with the food.

HIGGINS, Boston.

MEDICAL TREATMENT OF GASTROENTERITIS IN INFANTS. G. COCOZZA and R. FEROLA, Pediatria **59**:90 (Jan.) 1951.

Recent experience with 70 infants with gastroenteritis at the Pediatric Clinic in Naples has led to the conclusion that sulfonamide therapy is advisable for the milder cases, while the antibiotics streptomycin, chloramphenicol (chloromycetin®), and aureomycin were indicated in the severer cases, especially in dysentery.

HIGGINS, Boston.

TREATMENT OF INFANTS WITH GASTROENTERITIS IN MOUNTAIN AIR. I. VERONESE, G. FIORAVANTI, and S. CAVALIERI, Pediatria **59**:181 (March) 1951.

A mountain sanatorium for infants with diarrhea was established at an altitude of 1,100 meters, one hour's ride from Verona. Even although air conditioning had been installed at the main city hospital in Verona, the mortality was lower among infants cared for on the mountain—40% against 56% for the toxic diarrheas, and none as against 17% for the other acute diarrheas. The fever and diarrhea were of shorter duration on the mountain. The better light, including the actinic rays, the lower barometric pressure of about 100 mm. Hg, and the lower humidity may play a role in the better clinical and mortality records obtained for the mountain hospital.

HIGGINS, Boston.

ACUTE MESENTERIC LYMPHADENITIS IN CHILDREN. A. M. CAVALLOTTI, Pediatria **59**:219 (March) 1951.

The history of each of three cases of acute mesenteric adenitis was different, one case following pneumonia, another being in a child with a positive tuberculin reaction, and the third having no probable inciting antecedent cause. The symptoms may simulate appendicitis or enterocolitis. Two of the children had normal appendices when an exploratory laparotomy was performed. The other child was not operated on.

HIGGINS, Boston.

FLACCID DIAPHRAGM. LUIS VARGAS Y VARGAS and J. MARCELINO FIGUEROA C., Bol. méd. Hosp. inf., México **7**:670 (Oct.) 1950.

A presentation is made of four cases of diaphragmatic flaccidity in children whose ages ranged from 20 days to 5 months. There was a greater proportion of boys than girls. Also, the right side was more frequently affected. In all four pneumonia developed, and one of the patients also had vomiting episodes. In three the heart and mediastinum were displaced to the opposite side. Mortality was 50%, and the diagnosis was made by elimination.

FROM THE AUTHORS' SUMMARY.

CONTRIBUTION TO THE DIAGNOSIS OF CYSTIC FIBROSIS OF THE PANCREAS. GERTRUD OBERMEIER, Deutsche med. Wchnschr. **75**:929 (July 14) 1950.

Eight cases, seven of which were verified at postmortem examination, are reported; the absence of tryptic activity of stool is stressed and its contribution to the diagnosis mentioned.

AMBERG, Rochester, Minn.

CHYLOUS ASCITES IN EARLY INFANCY. RAIMUND GLANDE, Monatsschr. Kinderheilk. **97**:413 (Dec.) 1949.

This disease is usually present at birth and leads to weakness, vomiting, and dyspnea because of the accumulation of ascites. Paracentesis yields chylous fluid with varying fat content. It is postulated that it is due to functional immaturity of chyliferous vessel walls of the intestines. This may disappear during the first few months of life. Treatment is confined to abdominal paracentesis, which is often followed by spontaneous cure. Because of decreased utilization of foods, especially of fats, a high caloric diet is indicated.

HARTENSTEIN, Madison, Wis.

ENCOPRESIS. M. I. PRATT, Harefuah **38**:110 (April 3) 1950.

Encopresis is described as a condition analogous to enuresis—an involuntary passage of feces—and is considered a psychogenic disorder, in contrast to fecal incontinence, which usually has an organic basis. Encopresis is encountered in children of normal intelligence; no cases in girls have as yet been reported. The author considers the condition a conversion phenomenon—a neurotic modality of response to difficult situations, and occasionally to unconscious conflicts. He reports two cases. The first was that of a boy of 10 years with borderline intelligence who on being transferred to a school at some distance from his home, where the studies were somewhat beyond his capacity, manifested encopresis in reaction to his new difficulties by means of regression to the anal level. The second case is that of a boy of 9 years, one of four children, who at the age of 3 years had tuberculosis and was institutionalized for a short time. On returning home, he was unhappy, appeared dejected, and showed sibling jealousy. Enuresis and encopresis developed. He would put fecal matter in various places around the house. The enuresis and encopresis disappeared soon after he was returned to his previous environment.

N. SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Nervous Diseases

PRACTICAL ASPECTS OF MESANTOIN THERAPY IN EPILEPSY. JOSEPH L. FETTERMAN and VICTOR M. VICTOROFF, Am. J. Psychiat. **105**:410 (Dec.) 1948.

The authors stress that the aims in the treatment of epilepsy should be the reduction of the frequency of seizures rather than, as is often the case, the limitation of the daily number of pills

the patient may require. A good program of therapy includes the use of selected drugs with good psychiatric care.

A combination of methylphenylethyl hydantoin (mesantoin®) and diphenylhydantoin (dilantin®) sodium, in the authors' experience, is the most effective anticonvulsant. Side reactions of methylphenylethyl hydantoin are mainly drowsiness and skin eruptions. These are not severe. Somnolence may be counteracted with *d*-amphetamine (dexedrine®) sulfate, though many patients after a short period acquire a tolerance to methylphenylethyl hydantoin.

JAHR, Omaha.

A COMPREHENSIVE EVALUATION OF FIFTY CASES OF CEREBRAL PALSY. WILLIAM G. WOLFE, J. Speech & Hearing Disorders **15**:234 (Sept.) 1950.

Fifty cases of cerebral palsy selected at random from a file of 2,329 cases in the department of orthopedics of the University of Iowa Hospital were evaluated for type of cerebral palsy; orthopedic, pediatric, visual, otological, neurological, and psychological conditions, and speech. The general conclusions are that cerebral palsy is a condition in which there are multiple handicaps, that complete diagnostic services must be provided, and that any successful rehabilitation program must meet not only the physical needs of the cerebral palsied child but also his educational and psychological needs. Approximately 16% of these children need to be placed in special hospital schools where special physical rehabilitation and education can be carried on together; 38% of these patients can be educated in the public schools, if special orthopedic classes can be provided; and 26% are said to be not educable and must be cared for permanently in homes or institutions.

PALMER, Wichita, Kan.

LOCAL PARALYSIS IN CHILDREN AFTER INJECTIONS. J. K. MARTIN, Arch. Dis. Childhood **25**:1 (March) 1950.

Seventeen cases are described in which paralysis of a single limb occurred within 28 days after an injection. Of these, fifteen cases appeared after immunization and two after penicillin injections.

The etiology is discussed. The facts pointing to poliomyelitis are the constitutional symptoms, the changes in the cerebrospinal fluid, and the seasonal incidence.

The author discusses whether or not the trauma of an injection determines the site of maximum paralysis. It is concluded that there is a case for considering the suspension of immunization during an outbreak of poliomyelitis.

KELLY, Milwaukee.

A SURVEY OF RECENT DEVELOPMENTS IN THE TREATMENT OF PNEUMOCOCCAL MENINGITIS. W. P. U. JACKSON, Arch. Dis. Childhood **25**:22 (March) 1950.

An attempt has been made to trace the development of the recent therapy of pneumococcic meningitis and to note its effect in progressively lowering the mortality of this disease. A series of 163 cases occurring in Birmingham during the last 11 years has been analyzed. It is evident that the prognosis of pneumococcic meningitis in general is not as good as might be expected, although the causes of failure in therapy are not always obvious.

The special problem of diagnosis in the infant has been considered, since the signs of meningeal infection at this age are usually atypical and frequently misinterpreted. Recent trends in the methods of using penicillin are discussed, and it seems possible that very large doses of this drug given intramuscularly may obviate the necessity for intrathecal injections and the use of sulfonamide.

KELLY, Milwaukee.

INTRASPINAL PENICILLIN TREATMENTS IN PURULENT BACTERIAL MENINGITIS IN CHILDREN. M. BERNARDI and PINO MENGHI, Minerva pediat. **3**:153 (March) 1951.

Sixty-nine patients with purulent meningitis were treated in the Pediatric Clinic of the University of Milan in the three years of 1947 to 1949. From their experience with 51 cases of meningococcic meningitis, the authors report that even quicker recovery resulted as a rule with penicillin and sulfonamide medication when penicillin was not given intrathecally. However, of

11 patients with pneumococcic meningitis, eight recovered and one died when penicillin was injected intrathecally, while both of the patients who did not receive intraspinal therapy died. The one patient with syphilitic meningitis, the two with streptococcic meningitis, and one of the three patients with staphylococcic meningitis recovered with intrathecal treatments; but the one patient with influenza meningitis died. No untoward meningeal irritation was observed to result from the penicillin injections.

HIGGINS, Boston.

MENINGITIS DUE TO AEROBACTER IN A NEWBORN CHILD 4 DAYS OLD. P. REFINETTI, J. B. DOS REIS, and R. AIDAR AUN, Arq. neuro-psiquiat. **7**:299 (Sept.) 1949.

A 4-day-old boy cried inordinately for 12 hours and refused the breast. Examination revealed a slight icteric tinge, and the temperature was 36.6 C. (97.9 F.); the fontanel was tense, and crying was increased when the child's head was flexed. The Kernig and Brudzinski signs were not elicited; there were a red throat and bilateral otitis media, for which the drum membranes were incised. The child was placed under treatment with sulfadiazine immediately. He had three attacks of tremulousness and cyanosis during the night. A lumbar puncture was done a day later. The fluid was turbid, and the child was given penicillin therapy. Gram-negative organisms were found the next day, and intrathecal and intramuscular administration of streptomycin was added. The child did poorly in spite of the treatment with sulfadiazine, penicillin, and intrathecal, intramuscular, and intraventricular injection of streptomycin. During the course of the illness a complicating ventriculitis apparently developed, because, as the lumbar fluid cleared somewhat, the ventricular fluid showed increased cells and protein. After the first puncture the fluid continued to be hemorrhagic. The child did poorly and died after 17 days of illness. The authors point out the rarity of infection by Aerobacter in the newborn and emphasize the importance of culturing hemorrhagic fluids, especially of the newborn. They also stress the paucity of signs and objective findings in newborn children. The child died of hydrocephalus, probably due to ventricular block. Histologic examination of the brain showed evidence of meningoencephalitis; brain abscess was not found.

SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CASE OF MENINGITIS CAUSED BY SALMONELLA TYPHOSA AND TREATED WITH AUREOMYCIN AND CHLOROMYCETIN. PEDRO DANIEL MARTINEZ, LUIS GOMEZ OROZCO, and J. LUIS PEREZ NAVARRETE, Bol. méd. Hosp. inf., México **7**:701 (Oct.) 1950.

Presentation is made of a case of meningoencephalitis in which Salmonella typhosa was found to be the etiologic agent. Meningoencephalitis was suspected when Brudzinski's reflex was elicited in the patient, who already had typhoid.

Treatment was instituted with aureomycin and chloramphenicol (chloromycetin®), with no evident results. The patient improved progressively, but behavior and gait disturbances and signs of intracranial hypertension remained as sequelae.

FROM THE AUTHORS' SUMMARY.

Psychology and Psychiatry

GENESIS OF HOSTILITY IN CHILDREN. LAURETTA BENDER, Am. J. Psychiat. **105**:241 (Oct.) 1948.

Basing her statements on her 14 years' experience with problem children, the author repudiates Freud's earlier concept that aggression is hostile and is a primordial reaction to frustration, as well as his later concept that aggression is an instinctual drive equated with the death instinct.

Discussing some of her earlier observations that aggression in childhood is a symptom complex resulting from deprivations caused by developmental discrepancies in the total personality structure, Bender continues with new formulations:

1. The child has an inherent drive toward normality which is determined by biologic maturation. This drive is so great that it is hard to block or direct it by any pathologic change within the child or his outer milieu.

2. The child has an inborn capacity to relate to the mother or parent figure and by identification to experience the emotional things of life which make us all human beings.

3. The child is born with a capacity for internal fantasy life which follows the pattern toward maturation and interpersonal identification as well as its own pattern of symbol formation.

These psychologic traits are discussed in their relation to behavior as it applies to aggression and hostility.

JAHR, Omaha.

THE PSYCHOANALYTIC CONTRIBUTION TO THE TREATMENT OF BEHAVIOR PROBLEMS IN CHILDREN. SANDOR LORAND, Am. J. Psychiat. **105**:357 (Nov.) 1948.

The author presents a general discussion of the subject as it applies to the alleviation of problems in child behavior.

JAHR, Omaha.

THE VALUE OF THE RORSCHACH TEST IN DIFFERENTIAL DIAGNOSIS. REGINALD J. YOUNG, Am. J. Psychiat. **105**:381 (Nov.) 1948.

Discussing some of the more difficult diagnostic problems pertaining to the emotional states, Young recommends wider use of the Rorschach technique. It is essentially a laboratory tool in a category with the Binet-Simon test and the electroencephalogram.

JAHR, Omaha.

THE ROLE OF RHYTHMIC PATTERNS IN CHILDHOOD. REGINALD S. LOURIE, Am. J. Psychiat. **105**:653 (March) 1949.

Rhythm is a universal phenomenon well recognized as a part of biologic function. Its motor patterns, according to Lourie, serve as satisfaction to the instinctual needs, facilitating motor and ego growth and development. In the course of the utilization of this basic pattern, secondary factors arise, some of which afford relief of tension and anxiety. Repetitive movements yield pleasurable sensations (rocking, swinging, swaying, dancing).

This paper is a study of the observations on 130 children who presented more dramatic forms of rhythmic activity such as head banging, head rolling, or getting up on their hands and knees, rocking rhythmically back and forth. The youngest child began at 1 month; the latest onset was 2 years. In all, the movements were voluntary and without nystagmus, eliminating spasmus nutans and other involuntary head movements. With some these movements were transitory; in others they remained for months or years. The incidence is given as 10 to 20%, with 5% retaining the pattern until 2½ to 3 years of age. Occasionally it may be prolonged beyond this point. In the majority, as the children have grown older, the rhythmic patterns have changed in form instead of being dropped completely. Among the most prevalent substitutes are toe-curling, teeth grinding, ear pulling, nose rubbing, finger tapping, and skin scratching.

There is an excellent discussion of the genesis and nature of this bizarre habit pattern, with practical suggestions for therapy. In view of its incidence every pediatrician owes it to himself to read the article in the original form.

JAHR, Omaha.

THE EFFECT OF GLUTAMIC ACID UPON THE MENTAL AND PHYSICAL GROWTH OF MONGOLS. F. T. ZIMMERMAN, BESSIE B. BURGOMEISTER, and TRACY J. PUTNAM, Am. J. Psychiat. **105**:661 (March) 1949.

This paper presents a study of the effects of glutamic acid upon mentally retarded children, 30 of whom were classed as having Mongolism and an additional 30 as not having Mongolism. All the 60 subjects studied had an IQ below 80. Glutamic acid was administered in doses from 24 to 36 gm. daily over a period of six months. An average gain of eight months in mental age was observed in the mongoloid type, a gain which represents a higher rate than that expected in the child with normal intelligence. Individual point rises varied from 0 to 20 over the six-month experimental period. The gain in the nonmongoloid group was about one-half the rate of the mongoloid. Glutamic acid also had an accelerating effect on the height and weight of the mongoloid group beyond that expected for normal children.

JAHR, Omaha.

REACTIONS OF CHILDREN TO A HIGHLY PUBLICIZED CRIME AGAINST A CHILD. SOPHIE SLOMAN, Am. J. Psychiat. **105**:779 (April) 1949.

The crime under discussion is the kidnaping of a 7-year-old Chicago girl whose dismembered body was found 24 hours after her disappearance. The local radios and newspapers supplied all the time, space, and pathos their editors could feature. After seeing several children seriously affected by the sensational publicity, Sloman made a study of the general juvenile reaction to the crime. After interviewing many children and school teachers, she observes that children who feel secure pay little attention to the implications and that only those afflicted with anxiety and insecurity experience adverse reactions. Her conclusion is that "the facts brought out should carry some measure of reassurance, at least. . . . the sensational press. . . . probably is not doing any special harm except in the cases of very insecure children, where the effect may actually be a helpful one instrumental in getting psychiatric help for a child who is already basically disturbed."

JAHR, Omaha.

THUMBSUCKING: ETIOLOGY AND FREQUENCY. G. KLACKENBERG, Pediatrics **4**:418 (Oct.) 1949.

An investigation has been carried out to establish the frequency of thumb sucking and the importance of the sucking factor in the etiology. Thumb sucking and other comparable sucking occurred at the age level of one year in 50% of the patients. Among the 4-year-olds there was a frequency of 36%. These figures include both the mild and the severer degrees of thumb sucking. If only the latter are taken into account, the figure for the 4-year-olds is about 14%. One of the primary determinant factors in the appearance of the habit, so far as can be judged, is the degree of satiation in infants of the sucking activity. The probability of this appeared from comparisons of the mode of feeding. In any event, none of the children 4 years or older who had used a dummy teat (slightly more than 10% of the entire series) had ever been thumb suckers.

FROM THE AUTHOR'S SUMMARY.

STATISTICAL INVESTIGATION AS TO THE PROGNOSIS OF THE CHILDREN OF MENTALLY DEFICIENT MOTHERS. F. AUXILIA, Minerva pediat. **3**:9 (Jan.) 1951.

Of 482 children admitted to the Savona Orphanage in Italy, 49 were mentally retarded. Of these 49 children, 14 (7 premature) were children of normal mothers, 13 (3 premature) were of unknown parentage, and 22 (3 premature) were children of mentally deficient mothers. A group of 26 mentally deficient mothers had 33 children, 11 normal and 22 mentally deficient. Since illegitimate children of mentally deficient mothers are very often deficient also, and since these mothers may have more mentally deficient children, institutional care should be available for those mentally deficient mothers who have illegitimate children.

HIGGINS, Boston.

THE CHILD'S CONCEPTION OF THE "INDISTINCT" AS HE DEVELOPS. A. DALLA VOLTA, Minerva pediat. **3**:44 (Jan.) 1951.

This 35-page article deals with a new psychological avenue of approach in the evaluation of a child's mental development, namely, his conception of the "indistinct." This conception does not depend on memory as do so many tests, although variations in results will occur owing to different schools or family backgrounds. By "indistincts" are meant uniform and relatively unstructured situations, such as clear or cloudy sky, vast surfaces of sea or land, and things seen at a distance or with poor light. The child's conception is gathered by verbal questioning or by his drawing with colored crayons. The drawings of some of the children tested are included in the article. These drawings may extend into the imaginative field, although a child rarely of his own initiative brings in his religious conceptions (angels, paradise). This approach allows definite insight into the child's development, and establshment of norms may be possible. But caution must be followed in interpreting individual variations from what seems to be normal.

HIGGINS, Boston.

BENIGN LALLING IN CHILDREN. A. GISMONDI, Minerva pediat. **3**:98 (Feb.) 1951.

Lalling, or mispronouncing the letter R as an L, is very common in children of about 3 years of age. It is quite distinct from true stuttering and is usually soon outgrown. Treatment is best accomplished by establishing serenity in the home and avoiding noisy and emotional disturbances of the child. Occasionally it may be necessary to resort to adenoidectomy and tonsillectomy to improve the child's breathing.

HIGGINS, Boston.

Diseases of Ductless Glands; Endocrinology

TESTOSTERONE AND TISSUE RESPIRATION OF THE CASTRATE MALE RAT WITH A POSSIBLE TEST FOR MYOTROPHIC ACTIVITY. EUGENE EISENBERG, GILBERT S. GORDAN, and HENRY W. ELLIOTT, Endocrinology **45**:113 (Aug.) 1949.

Although the general metabolic effects of gonadal steroids have been recognized, the mechanisms by which they exert these effects are as yet poorly understood. The present experiment afforded the opportunity to study the effect of castration and testosterone upon muscle weight directly.

It was found that the oxygen uptake of liver, diaphragm, and levator ani is not increased, as it is in the brain, by castration.

Castration renders the diaphragm and the liver relatively insensitive to the oxidation-inhibiting property of testosterone, regardless of the presence or absence of glucose. A normal degree of reactivity is preserved in the castrate rat treated with testosterone.

Castration produces marked atrophy of the levator ani muscle of the male rat. Testosterone prevents this atrophy and in the doses used produces hypertrophy.

JACOBSEN, Buffalo.

THE EFFECT OF GROWTH HORMONE PREPARATIONS ON ALKALINE PHOSPHATASE OF THE TIBIA. JAMES C. MATHIES and O. H. GAEBLER, Endocrinology **45**:129 (Aug.) 1949.

Evidence that anterior pituitary growth hormone stimulates growth of bone is extensive. Since a relationship has been established between bone alkaline phosphatase and bone calcification, it appeared of interest to investigate the effect of growth hormone upon bone alkaline phosphatase in rats.

It was found that in immature hypophysectomized female rats the alkaline phosphatase concentration in the tibia is lower than in normal mature rats; it is greatly increased by maximal and submaximal doses of growth hormone.

The rise in tibia phosphatase concentration appears to be related to the increase in tibia weight resulting from treatment.

JACOBSEN, Buffalo.

ADRENAL CHANGES PRODUCED IN RATS BY INFECTION WITH B. TULARENSE AND B. COLI. GIFFORD B. PINCHOT, VIRGINIA P. CLOSE, and C. N. H. LONG, Endocrinology **45**:135 (Aug.) 1949.

It is well known that the adrenal glands respond to many infectious diseases by a depletion of their cholesterol content and that this indicates, along with a falling adrenal ascorbic acid content, a state of increased adrenal activity and, if advanced enough, of adrenal exhaustion. It is also known that infection with tularemia causes pathological changes in the adrenal glands and that these changes are compatible with the pathological picture of adrenal exhaustion.

The conclusion from the experiments here reported is that the adrenal hypertrophy and the profound fall in cholesterol content in rats infected with tularemia probably indicate a marked exhaustion of the glands by this disease.

JACOBSEN, Buffalo.

THE EFFECT OF ADRENAL CORTEX EXTRACT UPON URINARY NON-PROTEIN NITROGEN AND CHANGES IN WEIGHT IN YOUNG ADRENALECTOMIZED RATS. DWIGHT J. INGLE and MILDRED C. PRESTRUD, Endocrinology **45**:143 (Aug.) 1949.

The adrenalectomized rat is unable to grow at a normal rate. In the present study the authors have tested the suggestion that the slowing of growth in the adrenally insufficient animal is due

entirely to secondary changes, principally the reduction in intake of food. Adrenalectomized rats were given a constant caloric intake by stomach tube and received saline solution to drink. The administration of adrenal cortex extract was followed by a decrease in urinary nonprotein nitrogen and an increase in rate of gain in weight; these results were compared with those obtained from adrenalectomized rats which did not receive the hormone.

JACOBSEN, Buffalo.

EFFECTS OF UNDERFEEDING ON THIOURACIL ACTION IN RATS AND MICE. JOSEPH MEITES and I. P. AGRAWALA, Endocrinology **45**:148 (Aug.) 1949.

The ability of thiouracil to induce thyroid hypertrophy is believed to be mediated through a direct depression of thyroid hormone synthesis, thereby permitting increased thyrotropic hormone production by the anterior pituitary gland and greater stimulation of the thyroid. Underfeeding is believed to inhibit thyroid function through a direct depression of thyrotropic hormone secretion by the anterior pituitary gland. Thiouracil action therefore might be expected to be less effective in underfed than in normally fed animals, since the initial thyroid and thyrotropic hormone secretion rates would be lower than in normally fed animals.

The data presented here indicate that underfeeding does not reduce the response of the thyroids to a constant dosage of thiouracil in underfed rats and mice on a body-weight basis.

JACOBSEN, Buffalo.

EFFECTS OF A HIGH PROTEIN DIET ON THE ANEMIA INDUCED BY HYPOPHYSECTOMY IN ADULT FEMALE RATS, INCLUDING FURTHER DETAILS ON POSTHYPOPHYSECTOMY ANEMIA. ROGER C. CRAFTS, Endocrinology **45**:159 (Aug.) 1949.

In rats the anemia induced by hypophysectomy can be prevented by a high protein diet in combination with thyroxin and androgen therapy.

JACOBSEN, Buffalo.

TROPHIC HORMONES OF THE PLACENTA: FAILURE TO DEMONSTRATE THYROTROPHIN OR ADRENO-CORTICOTROPHIN PRODUCTION IN THE HYPOPHYSECTOMIZED PREGNANT RAT. MONTE A. GREER, Endocrinology **45**:178 (Aug.) 1949.

Results of these experiments indicate that neither thyrotropin nor corticotropin is produced in the hypophysectomized pregnant rat.

JACOBSEN, Buffalo.

THE EFFECT OF FOLLICLE STIMULATING HORMONE UPON OXYGEN CONSUMPTION OF CHICK OVARY SLICES. OLGA NALBANDOV and ANDREW NALBANDOV, Endocrinology **45**:195 (Aug.) 1949.

From the results of the experiments reported here, it appears that follicle-stimulating hormone affects some enzyme system or systems involved in oxidative mechanisms in ovarian tissue.

JACOBSEN, Buffalo.

FAILURE OF ADRENOCORTICAL EXTRACT TO MODIFY THE IMMUNITY ACQUIRED BY INTACT MICE THROUGH THE USE OF PNEUMOCOCCAL VACCINE. ERWIN P. VOLLMER JAMES and E. SAMSELL, Endocrinology **45**:204 (Aug.) 1949.

The low resistance of patients with adrenal cortical hypofunction (Addison's disease) and adrenalectomized animals to infection has led to speculation that adrenal function may influence the processes concerned with acquired immunity. These experiments were devised in order to ascertain whether or not adrenocortical hormones increase the immune response of intact animals to antigens. In all instances the results were negative, indicating that whole adrenocortical extract administered early in the immunization period did not modify the resistance of the animals to active homologous infection.

JACOBSEN, Buffalo.

A Study of the Origin and Distribution of the Antigonadotrophic Substance in Animals Chronically Treated with Crude Sheep Pituitary Extract. C. A. Ely, R. K. Meyer, and W. H. McShan, Endocrinology **45**:549 (Dec.) 1949.

The object of the work reported here has been to establish whether lymphoid tissue, or, more specifically, the lymphocyte, is the source and site of formation of the antigonadotrophic substance.

From the present report it must be concluded that so far as the antigonadotrophic substance may be considered to be an antibody the findings presented do not support the contention that lymphoid tissue is the source of the antibody, the rate of release of which is controlled by the secretions of the adrenal cortex, since it was not possible to demonstrate the antigonadotrophic substance in lymphoid tissues, nor was it possible to alter the antigonadotrophic titer of the blood serum of immune animals by adrenal cortex extract or lymph-node antiserum.

Jacobsen, Buffalo.

The Development of a Refractory State to Adrenocorticotrophic Hormone. Gilbert L. Gordon, Endocrinology **45**:571 (Dec.) 1949.

In view of the current interest in corticotropin (ACTH) and its widespread experimental use in the clinic and laboratory, it seemed pertinent to determine whether animals remain responsive or become refractory to repeated injections of this substance.

It was found that rats receiving repeated injections of purified hog corticotropin gradually became refractory to a test dose of the hormone which depleted consistently the adrenal ascorbic acid concentration of control rats. After seven weeks of corticotropin injections their response to the test dose was negligible. Serum from such rats contained a substance which consistently diminished the adrenal ascorbic acid depletion normally produced in the hypophysectomized rats by corticotropin.

On a body-weight basis the dosage level of corticotropin producing the refractory state in rats is comparable to that which has been used in man in the treatment of rheumatoid arthritis.

Jacobsen, Buffalo.

Diabetogenic Action of Purified Anterior Pituitary Hormones. Bernard A. Houssay and Evelyn Anderson, Endocrinology **45**:627 (Dec.) 1949.

This communication deals with the diabetogenic action of three of the anterior pituitary hormones: growth hormone, corticotropin (ACTH), and prolactin.

These experiments indicate that the growth hormone has a diabetogenic action on dogs, cats, and batrachians.

Jacobsen, Buffalo.

Attempts to Produce Diabetes in Guinea Pigs by Alloxan and Pancreatectomy. Jean Collins-Williams, Albert E. Renold, and Alexander Marble, Endocrinology **46**:1 (Jan.) 1950.

Although permanent diabetes has been produced in different ways in various species, it has not been reported in guinea pigs. This paper describes some attempts to produce diabetes in these animals.

It was found that in guinea pigs temporary diabetes with hyperglycemia and glycosuria of several days' duration developed following the daily intravenous administration of alloxan in dosage of 100 to 300 mg. per kilogram. Permanent diabetes could not be produced because of the narrow margin between the diabetogenic dose and the dose which produced marked anemia and fatal kidney damage.

Jacobsen, Buffalo.

A Comparative Study of Some of the Chemical and Morphological Changes Elicited in the Adrenals by Stress and Purified ACTH. Claude Fortier, Floyd R. Skelton, Paris Constantinides, Paola S. Timiras, Marc Herland, and Hans Selye, Endocrinology **46**:21 (Jan.) 1950.

The effects on the adrenal cortex of single and repeated injections of corticotropin (ACTH) were investigated and compared with the changes observed after exposure to acute systemic stress. It is concluded that corticotropin alone cannot account for the adrenal response during the alarm reaction.

Jacobsen, Buffalo.

SOME BIOLOGICAL PROPERTIES OF DESOXYCORTICOSTERONE GLYCOSIDE. ETHEL COSMOS, HELEN DUELL, and ROBERT GAUNT, Endocrinology **46**:30 (Jan.) 1950.

The glucoside of desoxycorticosterone is of considerable interest and possible usefulness because of its water solubility. Such a substance can be given intravenously, or if given by other means a faster absorption should be expected than with the commonly used desoxycorticosterone acetate in oil.

From these experiments, however, it is readily apparent that desoxycorticosterone glycoside does not approach the effectiveness of desoxycorticosterone acetate in the maintenance of life and growth in rats.

JACOBSEN, Buffalo.

ACTION OF INSULIN ON DEPOSITION OF GLYCOGEN AND STORAGE OF FAT IN ADIPOSE TISSUE. ALBERT E. RENOLD, ALEXANDER MARBLE, and DON W. FAWCETT, Endocrinology **46**:55 (Jan.) 1950.

Soon after the discovery of insulin, clinical observers reported the occurrence of atrophies. It has been shown that in insulin atrophies, the abnormal process consists in simple disappearance of fat without evidence of inflammatory reaction. In the search for an explanation of the effect of insulin on the adipose tissue of diabetics, the experiments here reported were devised.

It is concluded that insulin has a direct, local action on the adipose tissue at the site of injection. There is evidence to suggest that this may be due to a promoting action on the synthesis of fat from carbohydrate in the fat cell itself. The relation of these findings to the clinical occurrence of insulin lipodystrophies is discussed.

JACOBSEN, Buffalo.

THE EFFECT OF A STRESS UPON THE GLYCOSURIA OF PARTIALLY DEPANCREATIZED FORCE-FED RATS. DWIGHT J. INGLE, Endocrinology **46**:67 (Jan.) 1950.

The hypothesis that any severe stress should intensify diabetes by activating the adrenal cortices is based upon the following observations: 1. The secretory activity of the adrenal cortices is increased during most, if not all, types of stress. 2. Adrenal cortex extracts and steroids are diabetogenic. 3. Activation of the adrenal cortices by the administration of corticotropin (ACTH) intensifies diabetes.

The experiments here reported do not support the hypothesis that activation of the adrenal cortices during stress causes exacerbation of diabetes.

JACOBSEN, Buffalo.

THE EFFECTS OF STEROIDS ON THE INCIDENCE OF DIABETES IN RATS AFTER SUBTOTAL PANCREATECTOMY. J. T. LEWIS, V. G. FOGLIA, and R. R. RODRIGUEZ, Endocrinology **46**:111 (Jan.) 1950.

The experiments here reported indicate that the substances with estrogenic action decreased the incidence of diabetes which followed subtotal pancreatectomy in the rat, and the androgenic ones, on the contrary, increased it.

JACOBSEN, Buffalo.

FACTORS AFFECTING THE MEASUREMENT OF PROTEOLYTIC ACTIVITY OF THYROID TISSUE. MILDRED E. KAMNER, ANN PERANIO, and MAURICE BRUGER, Endocrinology **46**:353 (April) 1950.

Thyroid glands of adult dogs contain a factor in the presence of which tyrosine is formed from a hemoglobin substrate.

JACOBSEN, Buffalo.

THE PROTEOLYTIC ACTIVITY OF THYROID AND OTHER TISSUES OF THE DOG. MILDRED E. KAMNER, ANN PERANIO, and MAURICE BRUGER, Endocrinology **46**:359 (April) 1950.

If the organic iodine (diiodotyrosine and thyroxine) in blood plasma is derived from the thyroglobulin in the colloid of the thyroid gland, a mechanism is necessary to explain whereby these organic iodine compounds are split from the thyroglobulin molecule. The existence of a proteolytic enzyme in the thyroid capable of liberating diiodotyrosine and thyroxin from thyroglobulin, and thus allowing these smaller molecules to enter the blood stream, would offer such an explanation.

The progressive formation of tyrosine from a hemoglobin substrate in the presence of thyroid, spleen, liver, muscle, and blood was measured. The first three of these tissues exhibited proteolytic activity of a similar degree which was several times as great as that of muscle or blood.

JACOBSEN, Buffalo.

STUDIES IN THE DISTRIBUTION AND CONCENTRATION OF ALKALINE PHOSPHATASE IN THE ADRENAL CORTEX OF NORMAL AND OF SEX HORMONE TREATED PIGEONS. AMIYA B. KAR, Endocrinology **46**:363 (April) 1950.

The present studies have indicated clearly that there are considerable quantities of alkaline phosphatase in the avian adrenal cortex. Treatment with sex hormones causes a reduction in the cortical phosphatase activity. However, the degree of this reduction is more pronounced in birds receiving estrogen than in androgen-treated birds.

JACOBSEN, Buffalo.

EFFECT OF PROLONGED EXHIBITION OF DIETHYLSTILBESTROL ON PLASMA AND TISSUE LIPIDS IN THE CHICK. J. STAMLER, C. BOLENE, M. DUDLEY, and E. LEVINSON, Endocrinology **46**:375 (April) 1950.

Chronic exhibition of diethylstilbestrol to cockerels results in a sustained hyperlipemia, with an increased tissue concentration of cholesterol, phospholipid, and neutral fat. Body total cholesterol, phospholipid, and neutral fat concentrations are increased.

It has been suggested that "the fat absorbed into the blood is derived from the animals' fat deposits." The results of these experiments seem to disprove this. Diethylstilbestrol apparently influences lipid metabolism by effecting increased lipid synthesis, associated with normal or decreased lipid disposal.

JACOBSEN, Buffalo.

THE LIPOTROPIC ACTION OF DESICCATED THYROID IN THE CHOLESTEROL-FED CHICK. J. STAMLER, C. BOLENE, E. LEVINSON, and M. DUDLEY, Endocrinology **46**:382 (April) 1950.

Chronic cholesterol feeding leads to the development of a fatty liver in the chick. As in the rat, this fatty liver has a high content of both free and esterified cholesterol. Previous workers have shown that the cholesterol fatty liver is resistant to the lipotropic action of lecithin, choline, inositol, or lipocaic.

The present experiments show thyroid hormone to be highly effective in preventing the cholesterol fatty liver.

JACOBSEN, Buffalo.

CONVERSION OF DESOXYCORTICOSTERONE ACETATE TO PROGESTERONE IN VIVO. M. X. ZARROW, F. L. HISAW, and F. BRYANS, Endocrinology **46**:403 (April) 1950.

It has been known for some time that desoxycorticosterone acetate possesses progestational activity. The authors examined the serum of three castrated female monkeys and two normal male monkeys for progesterone levels by the Hooker-Forbes test before and after treatment with desoxycorticosterone acetate.

These experiments support the opinion that desoxycorticosterone acetate is converted to progesterone in the body and suggest an explanation for the progesterone-like action of desoxycorticosterone acetate.

JACOBSEN, Buffalo.

THE ROLE OF ESTROGEN IN THE ESTROGEN-RELAXIN RELATIONSHIP IN SYMPHYSEAL RELAXATION. ROY V. TALMAGE, Endocrinology **47**:75 (Aug.) 1950.

Experimental relaxation of the pelvic ligaments was first produced in the guinea pig by injecting serum of pregnant rabbits into animals which were in estrus. It was also found that extracts of corpora lutea of the sow would elicit a similar response. Later, it was shown that castrated guinea pigs were equally responsive provided they were pretreated with estrogen, but that in animals which were not conditioned by the previous action of estrogen, even very large doses of either pregnant serum or extract of corpora lutea were ineffective. The presence

of a hormone which has a specific effect on the pelvic ligaments was subsequently established and named relaxin, the effectiveness of which was dependent on the previous conditioning action of estrogen on the connective tissue structures.

The determination, therefore, of the changes produced by estrogen in the tissues of the symphysis pubis is essential for a complete understanding of the relaxation reaction.

It is found that water content of symphyseal tissue is raised 74%, interpubic distance increased 50%, calcium increased 100%, phosphorus decreased 40%, and alkaline phosphatase increased.

JACOBSEN, Buffalo.

DIRECT ACTION OF MALE SEX HORMONE ON THE ADRENAL CORTEX. LOUIS A. ZIZINE, MIRIAM E. SIMPSON, and HERBERT M. EVANS, Endocrinology **47**:97 (Aug.) 1950.

The interrelationship between the adrenal glands and the reproductive system has been well studied, experimentally as well as clinically, with regard to the influence of the adrenal glands on the sexual organs. The other aspect of the problem, the effect of the gonads on the adrenals, has not been given as much attention.

In these experiments it was found that testosterone propionate causes partial repair of the atrophied adrenal cortex of hypophysectomized rats, and also of that of the hypophysectomized rat which has been simultaneously gonadectomized. Therefore, the effect of the male sex hormone on the adrenal glands does not seem to be mediated through its action on the pituitary gland or the gonads.

JACOBSEN, Buffalo.

MECHANISMS OF DESOXYCORTICOSTERONE ACTION: EFFECTS OF THE WATER-SOLUBLE GLYCOSIDE ON HUMAN CIRCULATORY AND RENAL FUNCTIONS. D. M. GREEN, A. D. JOHNSON, W. E. BRIDGES, J. H. LEHMANN, and F. GRAY, Endocrinology **47**:102 (Aug.) 1950.

The effects of desoxycorticosterone glycoside on circulatory and renal function were studied in 13 human subjects. The renal action appeared to involve at least three effects: (1) an early, transitory rise in filtration rate; (2) a reduction in the tubular reabsorption of water, and (3) an alteration in sodium excretion. Continuous desoxycorticosterone glucoside administration was not associated with significant change in systemic blood pressure.

JACOBSEN, Buffalo.

THE EFFECT OF WATER AND POTASSIUM CHLORIDE INGESTION ON THE LEVEL OF URINARY 17-KETOSTEROIDS IN THE RABBIT. PATRICIA A. DANFORD and HAROLD G. DANFORD, Endocrinology **47**:139 (Sept.) 1950.

Much evidence indicates that adrenal cortical extracts and desoxycorticosterone acetate promote the excretion of ingested water and provide protection against lethal water intoxication in both normal and adrenalectomized animals. Furthermore, desoxycorticosterone has been found to be an effective stimulant for potassium excretion in the adrenalectomized animal. In view of these facts, one might expect the normal experimental animal to respond to excessive quantities of potassium or water with an increased production of adrenal cortical hormones, facilitating water or potassium excretion. The present investigation was undertaken in order to determine possible alterations in the excretion of 17-ketosteroids as a result of prolonged diuresis or excretion of excessive quantities of potassium.

Rabbits subjected to water diuresis for 48 hours excreted significantly greater quantities of 17-ketosteroids than did control rabbits, but there was not a consistent further increase in 17-ketosteroid excretion when potassium chloride was given. A significant positive correlation between urine volume and 17-ketosteroid excretion was found to exist.

JACOBSEN, Buffalo.

THE INFLUENCE OF ADRENAL CORTEX AND THYROID ON THE LOSS OF NITROGEN IN URINE AFTER EXPERIMENTAL BURNS. E. A. SELLERS, S. S. YOU, and ROSEMARY W. YOU, Endocrinology **47**:148 (Sept.) 1950.

After experimental burns an increase in the urinary excretion of nitrogen takes place, but conclusive evidence that endocrine factors are responsible or even implicated in the disturbance of nitrogen metabolism after injury is lacking. In this communication it is shown that nitrogen

loss after burning may usually be abolished or reversed by removal of the adrenals when the resistance of the adrenalectomized animals is increased by daily injection of desoxycorticosterone acetate.

Evidence is also presented which suggests that the thyroid gland is not causally concerned with the changes in protein metabolism which occur after burning.

JACOBSEN, Buffalo.

EFFECT OF THYROIDECTOMY, ADRENALECTOMY AND BURNING ON THE URINARY NITROGEN EXCRETION OF THE RAT MAINTAINED IN A COLD ENVIRONMENT. S. S. YOU, ROSEMARY W. YOU, and E. A. SELLERS, Endocrinology **47**:156 (Sept.) 1950.

An increased nitrogen excretion in the urine has been shown to occur after different forms of stress such as burning, traumatic injury, and exposure to a cold environment. The results of this investigation show quite definitely that an increased excretion of nitrogen in the urine occurs when rats are exposed to a temperature of 1.5 C. and that the increase is not dependent on the presence of either the adrenal or the thyroid glands. It may be concluded that the increased protein catabolism at this temperature may be affected by, but is not primarily due to, the action of the thyroid or the adrenal glands.

JACOBSEN, Buffalo.

THE LACK OF EFFECT OF THE ADRENAL HORMONES UPON GASTRIC ACID SECRETION. HORACE W. DAVENPORT and VIRIGNIA J. CHAVRE, Endocrinology **47**:193 (Sept.) 1950.

Many of the numerous physiological changes which occur in animals as the result of adrenalectomy are known to affect the ability of the stomach to secrete acid. Among these changes are a fall in blood pressure and cardiac output, a decrease in blood glucose concentration, a distortion of the plasma electrolyte pattern, and the occurrence of acidosis.

From the evidence here presented it is concluded that the hormones of the adrenal cortex play no direct or important part in the mechanism by which acid is secreted.

JACOBSEN, Buffalo.

TWO TYPES OF BASOPHILS IN THE ANTERIOR PITUITARY OF THE RAT AND THEIR RESPECTIVE CYTOPHYSIOLOGICAL SIGNIFICANCE. NCHOLS S. HALMI, Endocrinology **47**:289 (Oct.) 1950.

Two types of basophiles (beta and delta cells) can be distinguished in the pituitary gland of the rat by means of a new staining technique.

It is concluded that the delta cells are the most likely source of follicle-stimulating hormone and thyrotropin, while the possible role of the beta cells in the formation of corticotropin (ACTH) requires further investigation.

JACOBSEN, Buffalo.

STUDIES ON THE METABOLISM OF RADIO-PROGESTERONE IN MICE AND RATS. BYRON RIEGEL, W. L. HARTOP JR., and G. W. KITTINGER, Endocrinology **47**:311 (Nov.) 1950.

Metabolic studies related to the endocrinology of progesterone in mice and rats have been made with a labeled hormone. The hormone was not stored but was rapidly metabolized and excreted. The pituitary and adrenal glands of mice invariably contained relatively large concentrations of the injected radiocarbon. The highest concentration was observed in the pituitary gland of rats.

JACOBSEN, Buffalo.

THE GRADATION OF EFFECTIVENESS AND ABSORPTION OF DESOXYCORTICOSTERONE ACETATE PELLETS BY DILUTION WITH CHOLESTEROL. ALBERT SEGALOFF, Endocrinology **47**:320 (Nov.) 1950.

This experiment, in which both compressed and fused pellets of desoxycorticosterone acetate and cholesterol in varying percentages were employed, demonstrates that gradation in growth response in adrenalectomized animals can be obtained. It also shows that gradation in the rate of absorption is obtained which is roughly proportional to the percentage of desoxycorticosterone acetate in the pellets.

JACOBSEN, Buffalo.

Directory of Pediatric Societies *

INTERNATIONAL

International Pediatric Association

President: Dr. Felix Hurtado, Habana, Cuba.
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Next Meeting (Seventh International Congress of Pediatrics): Habana, Cuba, 1953.

International Congress for the Protection of Infancy

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Pan-American Congress of Pediatrics

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Time: Twelfth of every month, 8:30 p. m.

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Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

Australian Paediatric Association

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Time: One meeting a year.

British Paediatric Society

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Chinese Pediatric Society

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Time: Concurrent with the annual conference of the Chinese Medical Association.

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Place: Office of the Indian Medical Association, 67 Dharamtala St., Calcutta 13.
Time: Every second and fourth Wednesday of each month.

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Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norwegian Pediatric Society

President: Dr. Arne Njå, Oslo.
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Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

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President: Dr. A. G. Watkins.
Secretary: Dr. Ronald Mac Keith; Dr. J. J. Kempton.
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Place: Medical Society, Merced 565, Santiago, Chile. Time: 7 p. m., every Thursday.

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President: Dr. Miguel Fabres Izaga.
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Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

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President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
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Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

Sociedad de Pediatría de Córdoba

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Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.).
Place: Comite pro Defenso del Niño, Dean Fumes 2000. Time: Once a month.

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Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57.
Place: Colegio Médico. Time: Last Tuesday of every month.

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Secretary-Generale: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon, Portugal.

Sociedad Uruguaya de Pediatria

President: Dr. Conrado Pelfort.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

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President: Lya Imber Coronil.
Secretary: Dr. Guillermo Tovar, P. O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. **Time:** Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Paul Letondal, 370 E. Roy St., Montreal, Quebec, Canada.
Secretary-Treasurer: Dr. Edmond Baril, 301 Carré Saint-Louis, App. 1.
Time: First and Third Thursday of each month.

SOCIÉTÉ DE PEDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 Rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. **Time:** 4:30 p. m., third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE QUÉBEC

President: Dr. Roland Thibaudeau, 203 des Erables, Quebec, Que., Canada.
Secretary-Treasurer: Dr. Euclide Déchêne, 312 du Roi.

SOCIÉTÉ POLONAISE DE PEDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. K. A. Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent H. Magnusson, Sachs' Hospital for Children, Stockholm.
Secretary: Dr. M. d'Avignon, Norrtulls Sjukhus, Stockholm.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm and Pediatric Clinic Upsala. **Time:** Second Friday of each month (except summer).

THIRD SOUTH AMERICAN CONGRESS OF PEDIATRICS

President: Dr. Conrado Pelfort, Montevideo, Uruguay.

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 1 St. N. W., Washington, D. C.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester 7, N. Y.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Hugh McCulloch, La Rabida Jackson Park Sanitarium, Chicago.
Secretary-Treasurer: Dr. Aims C. McGuinness, 237 Medical Laboratories, University of Pennsylvania, Philadelphia.
Place: Hotel Chamberlain, Old Point Comfort, Va. Time: May 6, 7 and 8, 1952.

Canadian Society for the Study of Diseases of Children

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

Society for Pediatric Research

President: Dr. Horace Hodes, New York.
Secretary-Treasurer: Dr. Sydney S. Gellis, 300 Longwood Ave., Boston 15.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Henry E. Gallup.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Time: Four meetings a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N.W. Marshall St., Portland, Ore.
Secretary-Treasurer: Dr. Gorham Babson, 1107 S.W. 13th Ave., Portland, Ore.
Time: Two meetings a year, in March and September.

Northwestern Pediatric Society

President: Dr. J. Harry Murphy, 915 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elizabeth Lowry, 301 Kenwood Pkwy., Minneapolis.
Place: Minneapolis, St. Paul, Duluth, and Rochester. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. Joseph Lyday, 227 16th St., Denver 2.
Secretary-Treasurer: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of Denver or the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

Southwestern Pediatric Society

President: Chester I. Mead, 1930 Truxton Ave., Bakersfield, Calif.
Secretary: Dr. Clement H. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September, and November.

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6.

Arizona Pediatric Society

President: Dr. Carl A. Holmes, 1401 N. Seventh Ave., Phoenix.
Secretary-Treasurer: Jacob M. Sobol, 607 Heard Bldg., Phoenix.
Place: Phoenix or Tucson. Time: On Call.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Howard J. Morrison, 444 Drayton St., Savannah.
Secretary-Treasurer: Dr. J. Harry Lange, 490 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport

Louisiana State Pediatric Society

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

Medical Society of the State of New York, Pediatric Society

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Robert J. Mason, 308 N. Woodward Ave., Birmingham.
Secretary: Dr. Horace L. French, 301 Seymour Ave., Lansing.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Montana Pediatric Society

President: Dr. Edward A. Hagmann, 208 N. Broadway, Billings.
Secretary: Dr. George W. Nelson, 2814 Ninth Ave. N., Billings.
Place: Decided at each meeting—Spring and Fall.

Nebraska Pediatric Society

President: Dr. George J. Klok.
Secretary-Treasurer: Dr. Donald C. Nilsson, 115 N. 40th St., Omaha.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Hampshire Pediatric Society

President: Dr. Edward L. Tuohy, Manchester.
Secretary-Treasurer: Dr. William D. Penhale, Concord.

New Jersey Medical Society, Pediatric Section

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Rowena Sidbury Hall, 15 N. Fifth St., Wilmington.
Secretary-Treasurer: Dr. Katherine Anderson, 138 Hawthorne Rd., Winston-Salem.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September, and November.

North Dakota Pediatric Society

President: Dr. L. G. Pray, Fargo Clinic, Fargo.
Vice President: Dr. B. A. Mazur, Dakota Clinic, Fargo.
Secretary-Treasurer: Dr. William J. Ball, Northwest Clinic, Minot.
Place: Bismark.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. C. S. E. Touzel, 1111 Pennsylvania Ave., Fort Worth.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco.
Treasurer: Dr. Edith Bonnet, 228 Medical Arts Bldg., San Antonio.

Virginia Pediatric Society

President: Dr. E. Berkeley Neal.
Vice President: Dr. E. L. Kendig.
Secretary-Treasurer: Dr. W. A. Mitchell.
Executive Board: Dr. F. R. Hopkins and Dr. J. O. Rydeen.

Wisconsin State Medical Society, Section on Pediatrics

President: Dr. K. J. Winters, 1411 Wauwatosa Ave., Milwaukee 13.
Secretary: Dr. Niels L. Low, 744 Main St., Racine.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. Charles H. York, 10465 Carnegie Ave., Cleveland 6.
Secretary: Dr. Earl E. Smith, 10640 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February, and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St., W.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month,

Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33rd St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.

Bronx Pediatric Society

President: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Secretary: Dr. George Weiss, 790 Grand Concourse, New York 51.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Lewis A. Koch, 62 Pierrepont St.
Secretary: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn 17.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April. October, and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Pkwy.
Secretary: Dr. Richard A. Downey, 786 Forest Ave.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan Ave., Albany.
Secretary-Treasurer: Dr. Fred W. Bush, 26 S. Goodman St., Rochester.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. E. V. Turner, 2479 E. Main St., Columbus.
Secretary-Treasurer: Dr. Mary L. Scholl, 1384 Grandview Ave., Columbus.
Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka.
Secretary: Dr. Alfred S. Traisman, 6349 N. Clark St.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg.
Secretary: Dr. William F. Hunting, 6048 Montgomery.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dade County Pediatric Society

President: Dr. William W. McKibben, 641 N. Greenway Dr., Coral Gables, Fla.
Secretary-Treasurer: Dr. Wesley S. Nock, 671 N.E. 57th St., Miami 38, Fla.
Time and Place: Variable.

Dallas Pediatric Society

President: Dr. Fred Brooksaler, 4207 Lemmon Ave.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave.
Place: Children's Hospital of Texas. Time: 6:30 p. m., the first Thursday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Wilfred D. H. Nolting, 16840 E. Warren.
Secretary: Dr. Ruben Meyer, 938 Maccabees Bldg.
Place: Variable. Time: Five times annually.

FORT WORTH PEDIATRIC SOCIETY

President: Dr. Frank Cohen, 712 S. Henderson.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania.
Place: Welch and West Restaurant. Time: Third Friday of each month.

HONOLULU PEDIATRIC SOCIETY

President: Dr. Walter B. Herter, 305 Royal Hawaiian Ave.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu 14.
Place: At doctors' homes in rotation. Third Thursday of each month, 6 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Byron P. York, 3911 Montrose Blvd.
Secretary: Dr. David Schrum, 3207 Montrose Blvd.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg.
Secretary: Dr. Leland Speer, 1022 Hoel Pkwy.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LONG BEACH PEDIATRICS SOCIETY

President: Dr. Lynn B. Vaughan, 302 Cherry Ave.
Secretary-Treasurer: Dr. Sam S. Woolington, 541 E. Broadway.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd. Time: Second Monday of February, April, June, October, and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Irving S. Pearlman, 7602 Bay Parkway, Brooklyn.
Secretary: Dr. Irving Weinstock, 350 Ocean Ave., Brooklyn.
Place: Kings County Medical Society. Time: 8:45 p. m., fourth Monday of April, October, November, January, and March.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N. W.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E.
Place: Medical Society Bldg., 1718 M St. N. W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. A. L. Kastner, 1810 West Wisconsin Ave., Milwaukee 3.
Secretary-Treasurer: Dr. A. L. Babbitz, 606 West Wisconsin Ave., Milwaukee 3.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October, and December.

MOBILE PEDIATRIC SOCIETY

President: Dr. Daniel Sullivan, 109 S. Broad St.
Secretary: Dr. Robert O. Harris, III, 1514 Government St.

Nashville Pediatric Society

President: Dr. John M. Lee, Doctors Bldg., Nashville.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St.
Time: Third Thursday of every month.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Arthur F. Anderson, 122 E. 76th St.
Secretary: Dr. L. Emmett Holt Jr., 477 First Ave.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. T. F. McNair Scott, 1740 Bainbridge St., Philadelphia 46.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. J. A. Gilmartin, 3708-15th Ave.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Meyerson Coe, 217-02 91st Ave., Queens Village, N. Y.
Secretary: Dr. Moe Goldstein, 111-32, 76th Ave., Forest Hills, N. Y.
Place: The Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June. July, and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Donald L. Thurston, 500 S. Kingshighway, St. Louis 10.
Secretary-Treasurer: Dr. Leo F. Gowan, 337 W. Lockwood Ave., St. Louis 19.
Place: Candlelight House. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Santa Barbara Pediatric Society

President: Dr. Helen Hart, City Health Department, de la Guerra Plaza.
Vice President: Dr. Clarence Hills, 22B W. Micheltorena St.
Secretary-Treasurer: Dr. L. C. N. Wayland, 1235 Chapala St.
Meetings: Four times annually.

Seattle Pediatric Society

President: Dr. David M. Harris, Medical Arts Bldg., Seattle 1.
Secretary: Dr. William A. Jaquette Jr., 1305 Seneca, Seattle 1.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Fred J. Chapin, 101 John St., Bay City.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. A. O. Manske, 1917 Austin Ave.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave.
Place: 1917 Austin Ave. Time: Third Tuesday of each month.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

WESTERN MICHIGAN PEDIATRIC SOCIETY

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary-Treasurer: Dr. John C. Montgomery, 1810 Wealthy St. S. E., Grand Rapids.
Time: Meets on the first Wednesday in October, November, April, and May of each year. Two meetings are held in Grand Rapids and two in other designated localities.

WICHITA PEDIATRIC SOCIETY

President: Dr. Walter L. Schafer, 401 N. Emporia St., Wichita 2, Kan.
Secretary: Dr. William F. McGuire, 401 N. Emporia St., Wichita 2, Kan.
Place: Variable: Time: First Thursday of each month.

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*References:

1. Stokes, J., Maris, E. P., and Gellis, S. S., *The Use of Concentrated Normal Human Serum Globulin (Human Immune Serum Globulin) in the Prophylaxis and Treatment of Measles.* J. Clin. Invest. 23:531-550, 1944.

2. Karelitz, S., *Does Modified Measles Result in Lasting Immunity?* Jour. Pediat., 36:697, June 1950.

3. Stokes, J., *Use of Gamma Globulin from Large Pools of Adult Blood Plasma in Certain Infectious Diseases.* Ann. Int. Med., 29:958, 1947.

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1. Lewis, J. M., et al.: Jl. Pediatrics 31:496, 1947
2. Kramer, B., et al.: Am. Jl. Dis. Child. 73:543, 1947
3. Halpern, G. R., et al.: Science 106:40, 1947
4. Nutrition Reviews 5:286, 1947
5. Clifford, S. H. and Weiler, K. H.: Pediatrics 1:505, 1948
6. Popper, H., et al.: Gastroenterology 10:987, 1948
7. Davidson, D. M., et al.: Jl. Invest. Derm. 12:221, 1949
8. Nutrition Reviews 6:248, 1948

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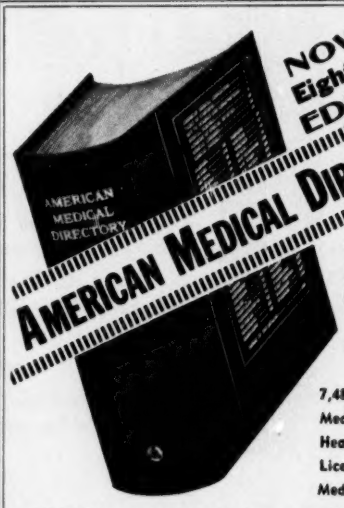

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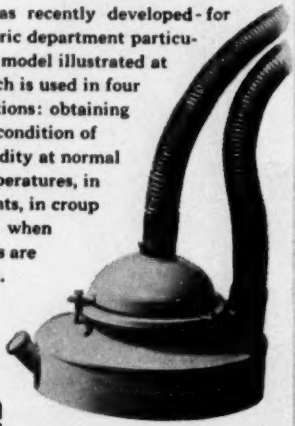

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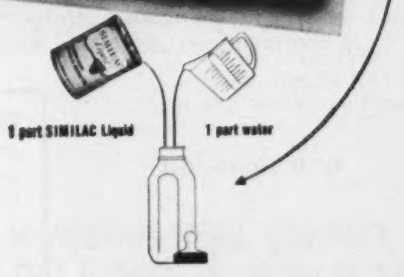

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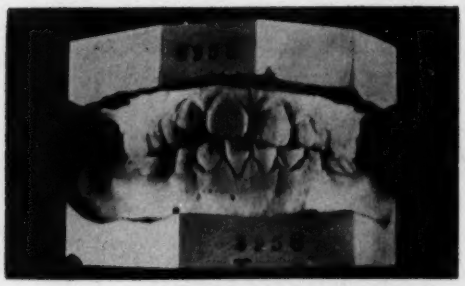

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References: 1. Am. J. Pub. Health, 30:182
2. Am. J. Pub. Health, 37:1113
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